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PRIMARY PULMONARY TUBERCULOSIS IN CHILDHOOD

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It is now a generally accepted opinion that tuberculous infection occurs, as a rule, through inhalation of tubercle bacilli. In whatever way the bacilli are inhaled, they finally lodge in an alveolus. There they multiply quickly and produce irritation of the alveolar epithelium. The anatomic result is a pneumonic inflammatory process. In occult cases the pneumonia affects only a few alveoli; in serious cases it may gradually involve the greater part of an entire lobe. Histologically regarded, the pneumonia does not have the appearance that is characteristic of tuberculosis. It can be recognized only by the presence of a great number of tubercle bacilli. This tuberculous pneumonia is called the primary focus; it is the first anatomic lesion in the organism produced by the infection.

Soon after the lungs have been infected, the tubercle bacilli spread from the alveoli along the lymphatics to the regional glands in the hilus. On the way to the hilus and in the glands they produce changes of the same nature as those in the lung. The primary focus, the tuberculous lymphangitis and the glandular lesions are called the primary complex.

To begin with, the tubercle bacilli do not encounter resistance in increasing and spreading, but later they are compelled to fight harder and harder against the defensive powers mustered by the organism. The forces mobilized under the influence of the infection are of two kinds. One type consists of phenomena that make the child less susceptible to new exogenous infections and enable it to restrict the infection in progress; the other, of phenomena that cause the organism to react more intensely to the bacilli and their toxins. The first type corresponds to immunity; the second to hypersensitivity or allergy (in a narrow sense).

The first histologic sign of incipient immunity is a wall of lymphocytes, which forms about the primary focus, while an area of caseous necrosis develops in the center of the lesion. So far, however, the reaction is inconsiderable. The change that it gives rise to can, anatomically, be discovered only after a thorough search of the lungs. Clinically, the lesion is not yet demonstrable. There are no subjective symptoms or change in the appearance of the child. He has no fever, does not feel

ill and looks perfectly well. No objective symptoms are demonstrable that can be referred to the developing disease. It is impossible to discover clinically by means of physical or roentgenologic examination or by tuberculin tests what is anatomically going on in the lungs and the glands of the hilus.

There is only one possibility at this stage of verifying clinically the tuberculous disease, and that is a laboratory method. As already pointed out, the primary focus is a pneumonic process harboring numerous tubercle bacilli. The pneumonic process is connected through the fine bronchial tubes with the larger bronchi and, through these, with the outer world. The tubercle bacilli in the primary focus can escape in this way and become clinically demonstrable. Children, however, usually do not expectorate but swallow the sputum. The bronchial mucus contains the tubercle bacilli, and the organisms can be demonstrated in the water from lavage of the stomach. This proof is not only theoretically imaginable but practically realizable. It was shown me for the first time six years ago in an infant observed in my Hospital. The patient was a 7 month old girl, who had been infected by her mother. About a week before sensitivity to tuberculin appeared, an examination of the water from lavage of the stomach gave a positive result. On this occasion the roentgenogram showed a normal appearance, and the girl did not react to large doses of tuberculin. Similar observations have since been reported by Sayé and Poulsen.

Seldom, however, does one have opportunity to examine a child during this stage of tuberculous infection. Usually, week after week passes without the child being ill or the disease being clinically demonstrable. The disease is in its period of incubation. By this term used in regard to tuberculous infection is understood the time that elapses between the penetration of the tubercle bacilli into the organism and the appearance of allergy. This interval is fairly constant and varies only from three to seven weeks.

The end of the period of incubation is thus marked by the appearance of allergy. This condition asserts itself anatomically in the following manner: A rather sudden and violent inflammatory reaction around the tuberculous focus takes place. This perifocal reaction, as regarded histologically, is not a typical tuberculous process of inflammation but consists of hyperemia with desquamation of alveolar cells, lymphocytic infiltration and edema. Here and there, however, occur minute necrotic foci and giant cells, thus indicating the etiologic origin of the pneumonic process. The same reaction is produced in the lymphatic glands, which increase rapidly in size.

At this stage of tuberculosis there is, consequently, often an extensive pulmonary lesion, in the center of which lie a usually small caseous focus. In the hilus are noted a number of lymphatic glands,

considerably distended, hyperemic and extremely edematous, often with periglandular edema and tuberculous foci of varying size. Tuberculosis has now manifested itself clinically as a disease, and this first manifest stage is called primary tuberculosis.

The pathognomonic clinical symptom indicating that this stage has been reached is the sensitivity of the child to tuberculin. Whereas before this time no reaction was produced by doses of tuberculin, however strong they were, the child now reacts to even relatively insensible doses of tuberculin, often markedly. As a rule, one may state that the sensitivity to tuberculin is high just at the time when allergy develops and is perhaps greater then than at any subsequent time. From this it follows that one can be content at this stage with comparatively insensible reactions to tuberculin in order to establish the diagnosis of a tuberculous infection. It is not necessary to inject the tuberculin intracutaneously in order to produce a sure reaction. The cutaneous Pirquet test or the percutaneous method with tuberculin ointment is sufficiently reliable.

I take it for granted that the Pirquet test is too well known to require elucidation. This test has the disadvantage of being somewhat painful, and it requires instrumentation. Under such circumstances, children are likely to be alarmed, and this of course should be avoided if possible. For this reason the test with tuberculin ointment is being used in Europe with increasing popularity. As regards reliability, the percutaneous method is as good as the cutaneous, provided it is performed in the right manner. As this tuberculin test is comparatively new and deserving of great attention, I will indicate briefly its most important points.

First, with regard to the choice of tuberculin ointment, I recommend the one made according to the formula of Professor Hamburger in Vienna, called "Hamburger's Perkutantuberkulin." It is sold in small tubes of 2 Gm. each. The test is carried out in this way: A small area of the skin over the sternum is carefully cleaned with cotton soaked in ether, and the skin is allowed to dry. Then a bit of the ointment about the size of a grain of rice is rubbed in with the finger on this area of the skin. The skin need not be covered after the ointment has been applied. In the negative reaction nothing happens; in the positive, a number of papular efflorescences appear. The reaction appears in the course of from two to five days and remains visible for about two weeks. This persistence may prove a distinct advantage in the case of practice among ambulatory patients, in which one may not have the opportunity of seeing the child again in exactly two days, which is necessary with Pirquet's test. The percutaneous test has, moreover, the additional advantage that the reaction can be read by the parents. This is not possible with other tuberculin methods. If nothing appears at the point

at which the tuberculin ointment was rubbed in, the reaction is said to be negative, and this result can be communicated over the telephone. If an eruption arises the child should come back for further examination. Heretofore, I have not seen a percutaneous test of this kind, properly carried out, which gave a negative result in a case of fresh primary tuberculosis.

A positive tuberculin reaction may be the sole clinical symptom of primary tuberculosis in the child. Under these circumstances the primary tuberculosis has not reached such a degree of advancement that it manifests itself as a disease. It is subclinical. In such cases the primary focus is small and the perifocal inflammation inconsiderable.

Most often, however, there arises another, though far more ambiguous, symptom besides the sensitivity to tuberculin, and that is fever. This rise in temperature does not show itself in a characteristic way. It resembles the ordinary fever accompanying a cold and is generally mistaken for one. It may sometimes be high, reaching 40 C. (104 F.). In other cases the fever may be only moderate. It may begin suddenly as in an influenzal infection, while in other cases the onset is much less violent. The course of the fever is also subject to wide variation. It may not be characteristic and may differ in no way from that seen in commonplace acute infections. The only thing that is fairly typical is the comparatively short duration.

Among 100 cases of children with manifest fresh primary tuberculosis who were observed at my hospital, the fever lasted not more than a week in 22 cases, from one to two weeks in 32 cases, from two to three weeks in 22 cases and more than three weeks in 20 cases. In the other 4 cases the course was afebrile throughout (fig. 1).

After the period of fever the temperature, as a rule, remains normal, unless complications set in. Occasionally, there is again a brief period of fever a few days or a week or so after the fall in temperature.

The fever that accompanies the development of primary tuberculosis is called initial fever or invasion fever and is entirely different from the febrile or subfebrile temperature of long duration that is usually associated with tuberculosis. In primary tuberculosis there is, on the contrary, transient fever with an acute beginning and a relatively short duration, followed by normal temperature. If a child with primary tuberculosis has a continued subfebrile or slightly febrile temperature, this usually points to a complicating commonplace infection. If the high fever continues long, for more than from four to six weeks, it is highly probable that malignant tuberculosis is developing.

Those who are not accustomed to seeing and diagnosing cases of primary tuberculosis in children do not recognize that fever of this kind may be the manifestation of the disease. In 99 of 100 cases the fever

is, in all probability, regarded as caused by a commonplace infection. It is easy to be led into a faulty diagnosis, because frequently a child shows signs of other infections at the same time that primary tuberculosis manifests itself. When sensitiveness develops to tuberculin and the allergy is high, a child often reacts with symptoms of illness due to a previously latent nonspecific infection. Such an infection flares up with the appearance of allergic reaction in the organism. The same phenomenon causes the appearance of allergy in a case of vaccination

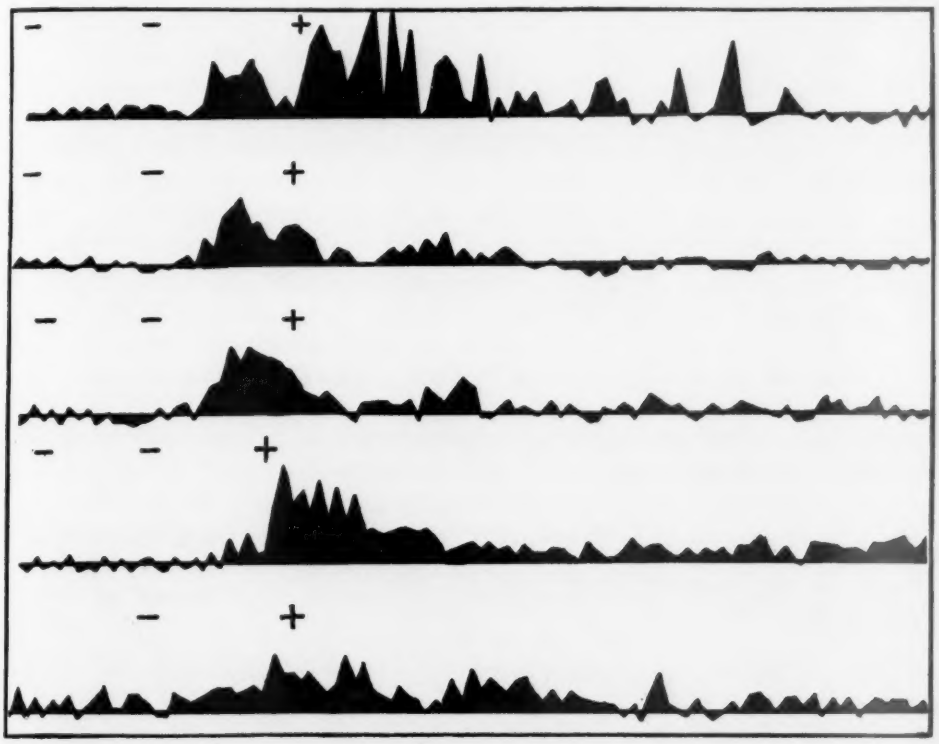

Fig. 1.—Temperature curves obtained from patients during the manifestation of primary tuberculosis. At the point marked —, the reaction to the Mantoux test with 0.1 mg. of tuberculin was negative; at the point marked +, the reaction was positive. The short duration of the fever and the normal temperature before and after the fever are to be noted.

for smallpox to be accompanied sometimes by angina. This is why one can rather often verify nasopharyngitis or other catarrhal disease of the upper respiratory tract at the first appearance of primary tuberculosis. One is tempted to think that the whole illness and fever are to be explained by such a nonspecific catarrh and may therefore easily overlook the more important fresh primary tuberculosis.

The only possibility of guarding against a diagnostic mistake is to make a point of carrying out a percutaneous tuberculin test on all children with fever. This holds good especially if the fever does not seem to be satisfactorily explained after careful examination of the child. If the reaction to the percutaneous test is positive, it is probable that the fever, at least in part, is caused by tuberculosis. If a child with an old, latent tuberculous infection contracts an acute febrile disease, the reaction to the percutaneous test is often negative, owing to the lowered sensitivity to tuberculin produced by the fever. In such cases the reaction becomes positive again if the test is repeated when the fever has disappeared. It is well known that measles greatly reduces the sensitivity to tuberculin. The same effect is also produced in varying degree by pertussis, influenza and the common cold.

It is not yet known whether the catarrhal phenomena are the expression of allergy or are to be regarded as a complication. Neither is it known whether the fever in cases of primary tuberculosis which are accompanied by a catarrhal disease is due to primary tuberculosis or to the concomitant nonspecific disease. This does not, however, matter much. The principal task for the physician is to avoid overlooking the primary tuberculosis, and knowledge of the frequency of the existence of catarrhal diseases in cases of developing primary tuberculosis guards him from diagnostic mistakes.

As I have already pointed out, every case of primary tuberculosis does not begin with fever. Well experienced observers in many cases have not been able to detect a rise of temperature when the sensitivity to tuberculin began. It must not, therefore, be presupposed that primary tuberculosis necessarily manifests itself with fever. But fever does occur frequently and is one of the most important aids in diagnosing the disease.

To recognize invasion fever as such is possible only on the condition that tuberculin tests are made. There is, however, a characteristic and easily recognizable symptom which serves as an indicator of the kind of fever present; that symptom is erythema nodosum.

It was a long time before the physician learned to interpret erythema nodosum correctly, and only during the last ten or fifteen years has its nature been elucidated. It has come to be seen more and more clearly that this syndrome stands in intimate connection with tuberculosis. This relation had long been conjectured by some authors but denied by the majority, who pointed out how rarely erythema nodosum occurs in such a common form of tuberculosis as phthisis, or generally speaking, in the patients who are already tuberculous.

It was the pediatrician who demonstrated the nature of erythema nodosum as the expression of tuberculous disease. There is only one opinion among pediatricians in Scandinavia, for example, as to the

correctness of this interpretation. However, one must not consider erythema nodosum as a symptom that is pathognomonic of tuberculosis. This is not the case. The syndrome is in itself nonspecific and may occur even in children who do not react to tuberculin. In such cases it stands to reason that it must be caused by another agency than tuberculosis. This rarely happens, however. In Sweden not more than 3 children of 100 with erythema nodosum give a negative reaction to tuberculin. In most other countries, the occurrence of erythema nodosum on a tuberculous basis seems to be less frequent.

If a child is examined before the erythema appears, it is found to react negatively to tuberculin. Even with high concentrations of tuberculin the reaction remains negative if the test is made before the appearance of the fever that accompanies erythema. But after the onset of fever the child reacts even to tuberculin tests with low concentrations. My associates and I had an opportunity of examining 75 children with cases of erythema nodosum before they fell ill. Of this group every child showed a negative reaction before the prodrome of fever and a positive reaction after its appearance.

From this observation it follows that erythema nodosum arises just at the time when the organism has become sensitive to tuberculin. In a number of cases in which the date of tuberculous infection was known, it was possible to establish by evidence that the interval between that date and the beginning of erythema was exactly coincident with the period of incubation of tuberculosis. This coincidence signifies, consequently, that the syndrome is coincident with the manifestation of primary tuberculosis and that the fever which accompanies erythema actually represents the invasion fever of tuberculosis.

This fact constitutes the great diagnostic value of erythema nodosum. If erythema nodosum arises in a child, he should be regarded as infected with tuberculosis, at least until a negative reaction to tuberculin has proved the contrary. The physican who omits to apply the tuberculin test to a child with erythema nodosum lays himself open to blame. He is ignoring the sign-post afforded by the erythema, which indicates that the fever in the child comes, in all probability, from tuberculosis. The presence of erythema nodosum not only permits the conclusion that tuberculous infection exists, but it should also make one suspect that the infection is in the primary stage.

Compared with the frequency with which erythema nodosum appears at the onset of primary tuberculosis, it is a rather rare syndrome when this phase of tuberculosis has passed. For my part, I have not noted it more than 20 times among more than 750 cases of erythema nodosum in children. The fact that erythema occurs just as the allergy develops has caused it to be interpreted as an expression of the allergic reaction. When erythema appears in those who are already tuberculous, it is

almost always preceded by an acute infection or some other factor that affects the existing allergy. For example, if a tuberculous child is taken ill with measles the sensitivity to tuberculin is considerably diminished. Subsequently, however, when allergy again appears, the same phenomenon occurs as with the first development of allergy in primary tuberculosis. The conditions for erythema nodosum to arise are thus present, and therefore the syndrome is sometimes seen to appear in children who are already tuberculous in connection with a new development in allergy.

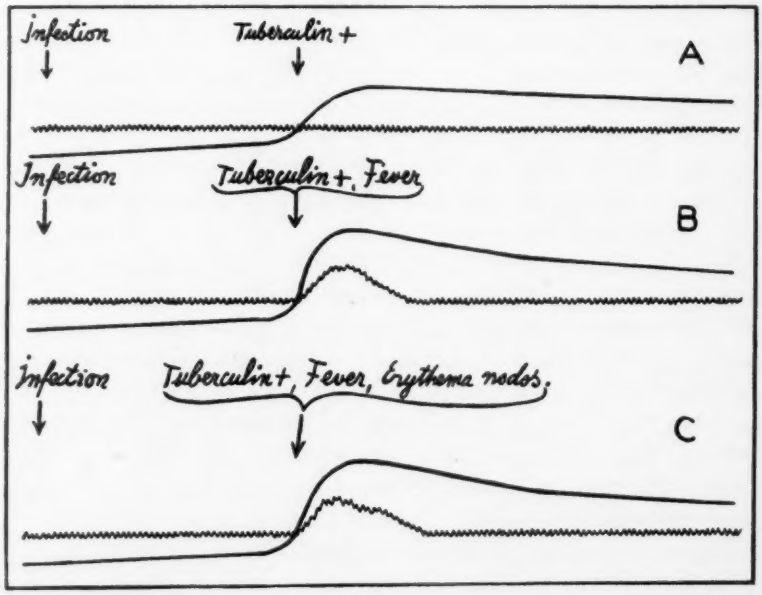

Fig. 2.—Scheme showing three forms in which primary tuberculosis may appear. *A* represents the type with a positive reaction to tuberculin only; *B*, that with a positive reaction and fever, and *C*, that with a positive reaction, fever and erythema nodosum. The wavy line marks the curve for changes in temperature; the straight line, the curve showing the manner in which allergy developed. The points designated as *a*, *b* and *c* indicate the periods at which allergy or fever appeared.

From what has been said it follows that primary tuberculosis may begin in three ways, which are illustrated in figure 2. Sometimes primary tuberculosis reveals itself in no other way than by a positive reaction to tuberculin. Most commonly, in all probability, fever arises coincident with the development of allergy. Finally, a number of children have erythema nodosum as well as fever. As both the fever and the erythema are expressions of a strong reaction in the organism, it is an obvious conclusion that it is the degree of the allergic reaction

and the rapidity with which it appears that determine whether the child will be affected by fever and cutaneous eruption.

If this view is correct, a slowly developing allergy which does not reach a high degree should be observed in children with fever-free primary tuberculosis. In the two other groups of children the rise of allergy at the end of the period of incubation is more acute and the degree of allergy high. The result is fever and, moreover, erythema nodosum in those especially disposed to it. In figure 2 are illustrated the different ways in which allergy may arise in the different groups of children.

It is especially in the last two groups that a marked perifocal allergic reaction arises around the tuberculous foci. With this appearance, the tuberculous infection has become tuberculous disease. Fortunately, a large number of children react as do those in the first group shown in figure 2, and here the perifocal reaction is, as a rule, so slight that it practically never, either subjectively or clinically, strikes one as indicative of disease. These children are therefore of little interest from the point of view of tuberculous disease during the primary stage. They are to be regarded as healthy. So much the more interest must be devoted, on the other hand, to the two other groups of children. It is among them that primary tuberculosis is found as a disease.

The physical symptoms of pulmonary primary tuberculosis are meager. This goes without saying, for the primary complex usually lies so deep intrathoracically that it is not accessible for percussion and in itself gives no auscultatory phenomena. However, when there is a marked perifocal reaction about a superficially situated primary focus, the process may be physically demonstrable and reveal itself as a pneumonic infiltration with dulness and bronchial murmur. When the process is a little more deeply situated, a weakening of the respiratory murmur may sometimes be heard over the affected area.

As a rule, however, the physical examination yields only negative results in primary tuberculosis. Even with the most minute percussion and auscultation, nothing that deviates from the normal conditions can be found. One is amazed, therefore, after the negative results of the physical examination, to find such definite roentgenologic changes as the accompanying figures show. I wish to emphasize that these exceptions are not rare, as surprises like these are met daily in a department for tuberculous children (figs. 3 and 4).

As the usual methods of examination leave one in the dark, it is not to be wondered that attempts have been made to work out new devices for examination. Such methods have been published now and again, but none of them is reliable. They may indicate pathologic lesions when none are present or normal conditions when tuberculosis of the bronchial glands really exists.

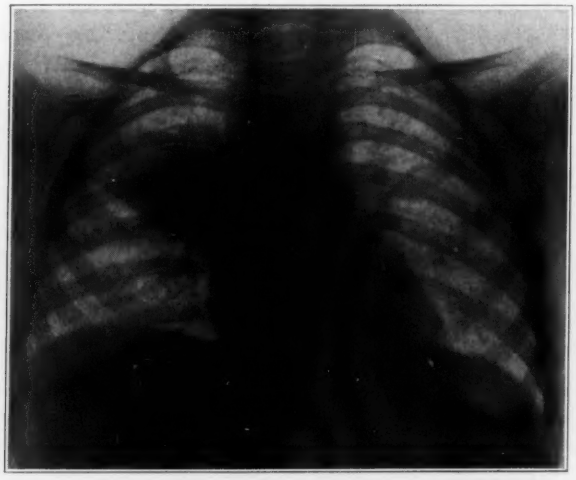

Fig. 3.—Roentgenogram of a child with primary tuberculosis, in whom the physical signs were negative, the roentgenographic findings positive and the reaction to tuberculin positive.

Fig. 4.—Roentgenogram of a child with bilateral primary tuberculosis without physical signs.

The methods of physical diagnosis of pulmonary primary tuberculosis are thus imperfect. The disease, as a rule, would not be localized clinically were it not for the roentgenologic examination at one's disposal. The perifocal inflammatory reaction appears roentgenologically as a more or less dense shadow which is somewhat diffusedly defined against the surrounding pulmonary parenchyma. Under all circumstances there are enlargement and densification of one or both of the hilus shadows. That which appears as an enlarged hilus shadow consists partly of the swelling of a bronchial gland, partly of a perifocal reaction in the pulmonary parenchyma itself projected to the same spot. If the pulmonary perifocal reaction lies behind, in front of or near the hilus itself, its roentgen shadow must fuse with the shadow produced by the swelling of the bronchial gland (fig. 5).

There is nothing pathognomonic in the roentgenogram of fresh primary tuberculosis. A reliable diagnosis of primary tuberculosis cannot, therefore, be made by means of roentgenologic examination alone.

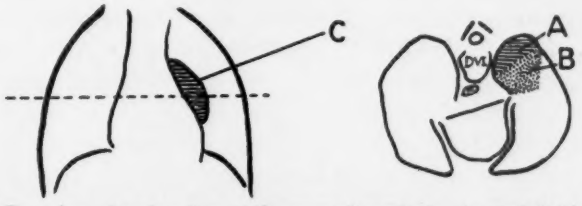

Fig. 5.—Drawing showing how primary tuberculosis situated behind the hilus may give a hilus shadow. *A* represents the primary focus; *B*, the perifocal reactions, and *C*, the enlargement of the hilus shadow.

If the symptoms otherwise point to the disease, the physician can, with its help, discover whether the process is localized intrathoracically and, in such case, the extent of the lesion.

The symptoms I have hitherto mentioned are those that are of most usual occurrence in cases of primary tuberculosis. During the most acute state the fever may, of course, be accompanied by subjective troubles—lassitude, headache, disturbed sleep, etc. One might also expect to find various symptoms arising from the respiratory passages. As a rule this is the case only in the children in whom manifestation of primary tuberculosis is accompanied by an acute catarrhal disease. In certain cases, however, there may appear two respiratory symptoms of diagnostic value, expiratory stridor and bitonal cough.

The expiratory stridor is typical. It is, as the term indicates, expiratory and often audible even at a certain distance. It troubles the child little, being more audible than productive of subjective discomfort. Clinically, however, it may appear threatening, and I once saw a colleague, ignorant of the origin of the stridor, attempt intubation in the

belief that the symptom of choking was dangerous. The stridor is caused by compression on contiguous bronchi provoked by glandular swellings in the hilus. Compression may be so great that atelectasis is produced in the corresponding part of the lung, which in its turn further complicates the picture. The more yielding the bronchi, the more easily does compression come into existence. Consequently, expiratory stridor is commoner in infants than in older children. It may, however, occur in children up to the age of 4 or 5 years.

The other respiratory symptom which is characteristic of cases of primary tuberculosis in infants is a peculiar cough called bitonal cough. If the sound of an ordinary cough is analyzed, it is found to consist, broadly speaking, of a single note produced in the larynx. In cases of swelling of the bronchial glands in infants, it often consists of two notes—a lower one corresponding to the usual sound of coughing and a higher one that arises as the air, during the act of coughing, passes through a narrowed passage in the bronchus. This so-called bitonal cough is, therefore, also a symptom of bronchial compression. I may add that, of course, neither this symptom nor the expiratory stridor is pathognomonic of swelling of the bronchial glands in cases of pulmonary primary tuberculosis. The symptoms may be present, although seldom, in nonspecific pulmonary diseases.

I now come to the course of pulmonary primary tuberculosis. The disease is generally benign. It heals, as a rule, with calcification of the primary complex, for the completion of which an average of at least three years must be reckoned on. How quickly primary tuberculosis completes its course from its manifestation to calcification depends, *inter alia,* on the size of the perifocal inflammatory process, but more particularly on the degree of the central caseous necrosis. The age of the child also plays a great part. The younger the child, the slower the healing.

It is scarcely possible to predict the course that a certain infiltration will take—whether it will follow the usual slow regression or whether it will become rapidly caseous and cavernous and with that pass over into progressive primary tuberculosis. The second form of the disease need not necessarily lead to death. Progress may cease at any moment, and the tuberculous tissue may heal. Healing takes place with sclerosis and calcification and with contraction of the involved part of the lung. Calcification as the final healing process of tuberculous tissue is considerably commoner in children, especially in infants, than in adults.

It is hazardous to attempt to predict in advance the course of the infiltration and the fate of the child. There are infiltrations of tuberculous etiology and great extension which recede entirely without caseation or contraction. The infiltration as seen roentgenologically then consists of noncaseous perifocal inflammation. The extent of the change

as it shows itself on physical or roentgenologic examination is, therefore, not the sole determinant of its further development. Nevertheless, the probabilities of a malignant course are greater with a large infiltration than with a small one. High and protracted fever and the results of the sedimentation test point to caseous changes involving a considerable area. To some extent this test enables one to follow what happens in the organism in a case of primary tuberculosis and also, although with considerable reservation, to draw prognostic conclusions. The presence or absence of bacilli obtained by means of washing out the stomach and the results of testing a guinea-pig with the water from lavage must not be taken to have prognostic value, as the majority of patients with active primary tuberculosis have open tuberculosis, and these lesions generally heal.

Having now touched on the more important points in the clinical examination of patients with pulmonary primary tuberculosis during its active phase, I will add a few therapeutic suggestions. In the main, the treatment is the same as that for adults with pulmonary tuberculosis, that is, fresh air, rest, suitable diet and the avoidance of all injurious influences.

There are, however, physicians who consider that no other precautions are required than those called for in the case of any other acute febrile disease. When the temperature is normal once more, the disease is regarded, practically speaking, as arrested, and no special notice is taken of the roentgenologic changes unless they affect the general condition of the child. These physicians are of the opinion that the patient will be cured of the disease in any case. To support such a view the experience is adduced that a large number of cases of primary tuberculosis remain undiscovered during the fresh stage and the lesions are later evident as calcified foci.

It is true that primary tuberculosis usually heals with no special treatment without the disease having been recognized in its initial stage. But from this it does not follow that a patient with fresh primary tuberculosis diagnosed as such shall not be treated. The sooner the process heals the better, and the healing, one presumes, is favored by the tissues being afforded the best possible conditions.

Like all other inflammatory processes, tuberculosis is favorably affected by allowing the sick part or organ to rest as much as possible. This means, as applied to a case of pulmonary primary tuberculosis, that pulmonary respiration must not be strained. The less bodily movement, the more rest for the lungs, and rest in bed guarantees the minimum of bodily movement. This may be regarded as the most important measure during the most acute stage. How long the child should be kept in bed is debatable. In my opinion he should be kept in bed as long as the disease has a general effect on the organism. If he is allowed

up too early, he will be limp, pale, tired and without appetite. The fever is one indicator, but a somewhat unreliable one, of how long the disease affects the organism in its entirety. A more refined index is the blood sedimentation test.

I take it for granted that the principles of the sedimentation test are known, as this method is now in common use everywhere. As regards children, especially when the test must be carried out often, as in the control of primary tuberculosis, it does not do to puncture a vein in making the test. But there are serviceable methods in which a few drops of blood obtained by puncturing the finger-tip is sufficient. With a little practice in this method one can obtain values as serviceable as those obtained with venous puncture. A handy apparatus for this purpose is mentioned by Landau (Microsedimentation [Linzenmeier-Raunert Method], *Am. J. Dis. Child.* **45:** 691 [April] 1933) and has been thoroughly tested at my hospital.

The rise in the blood sedimentation rate, like the fever, is a nonspecific phenomenon and like it may be provoked by commonplace infections. An infection of this kind in a tuberculous child causes a rise in the blood sedimentation rate, which consequently need not be due to tuberculosis as such. If the sedimentation test is taken as a guide in judging the status of the child and the primary tuberculosis, the possibility must therefore be rejected that the increased sedimentation rate is caused by any other factor than tuberculosis. Consequently, it is only by taking all other factors into consideration that the sedimentation test can be used in judging the condition of the tuberculosis. If one is acquainted with its possibilities, one can make good use of it, not least in judging the degree of rigorousness with which the patient should be treated.

If the sedimentation test is to be of any value it must be repeated at certain intervals; my associates and I make a test every week during the first stage of primary tuberculosis.

As I have just stated, the child should generally be kept in bed until the sedimentation rate has become normal. The time varies considerably in different cases, depending on the size of the infiltration, the general health, the degree and length of the febrile period and the age of the child. On an average, the necessary time of rest in bed is from four to six weeks after the fever has disappeared. The child should then be allowed up to some extent, the time being still determined by the temperature and the results of the sedimentation test, and not until these remain at normal levels, even if the child has been allowed out of bed for the greater part of the day, can the most acute stage of primary tuberculosis be considered past. Children of school age must not return to school until they show, under controlled conditions, that

they can be up and about and take exercise of the usual kind without an increase in the sedimentation rate.

I will first show how the sedimentation test proceeds in a case in which primary tuberculosis heals in the usual manner. A high sedi-

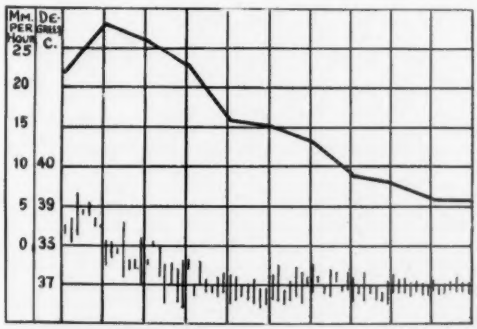

Fig. 6.—Graph demonstrating the course of the fever and the changes in the blood sedimentation rates (unbroken line) in a case of primary tuberculosis healing in the usual manner. The normal value of the blood sedimentation rate is about 7 mm. per hour.

Fig. 7.—Roentgenogram of the lungs of the patient from whom the values shown in figure 6 were obtained.

mentation rate is found not only during the stage of fever but also long after the fever has disappeared. The sedimentation rate gradually becomes less and less, until after a month or so the normal value is reached (figs. 6 and 7).

In a case of a less mild form of primary tuberculosis, the sedimentation value remains high for months after the fever has disappeared (figs. 8 and 9).

In addition to confinement in bed, the treatment requires an open air cure as nearly similar as possible to that of the sanatorium regime. There is no need to outline this in detail.

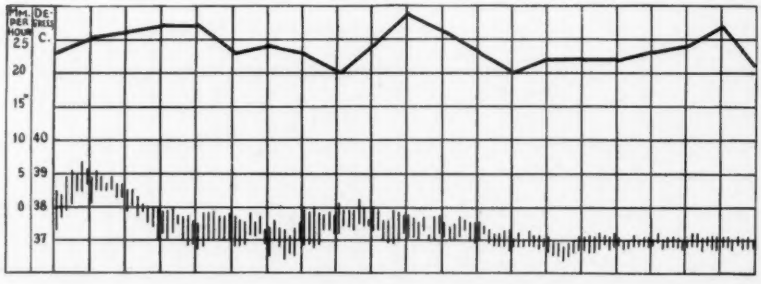

Fig. 8.—Graph showing the course of fever and the changes in the blood sedimentation rates in a more malignant type of primary tuberculosis in which pleurisy later developed.

Fig. 9.—Roentgenogram of the chest of the patient from whom the values shown in figure 8 were obtained.

A question that may be touched on is that of the indications for hospital treatment in cases of primary tuberculosis. This is in part a social and psychologic question. Strictly speaking, there is no necessity for hospital care in the case of a child with primary tuberculosis when the conditions in the home are what they should be. But if there are

infants in the same home who react negatively to tuberculin it is a wise precaution to let the possible risk of infection indicate hospital care for the sick child, during the first few months at least. There is, however, no concensus as to what importance from the point of view of infection shall be attributed to the circumstance that tubercle bacilli are present in the water from lavage of the stomach. Tests made on children with fresh primary tuberculosis and concomitant pertussis at this hospital show that tubercle bacilli may be expectorated and that the children are thus infectious, but this does not seem to be the rule. In any case, one may be tolerably certain that the risk of infection is slight, if indeed there is any, from a child that does not cough.

But even with the most favorable conditions at home, a neuropathic child is better away. The extent to which the child can be induced to remain in bed may serve to indicate whether he should be cared for at home. In such cases, as is well known, a change of environment has an exceedingly favorable effect.

The general treatment for primary tuberculosis also includes treatment with sunlight or artificial light. A number of authorities have given their opinion that treatment with ultraviolet light during the initial stage of primary tuberculosis may activate the process. For this reason I have, no doubt with many others, postponed the light treatment to a more advanced stage. The light treatment, then, does not begin until a few months have elapsed, and this therapy is continued periodically during the winter. During the summer, it is advisable for the child to be at the seaside or in the highlands.

A question I cannot avoid raising is that of the local treatment of pulmonary primary tuberculosis. One might think it suitable to treat the patients with large perifocal infiltrations with pneumothorax, and this has been done in certain places. For my part, I have never applied pneumothorax to patients in this stage of tuberculosis, and I have never had occasion to regret the policy. The tuberculous process has healed well without it. With few exceptions I think pneumothorax therapy in cases of primary tuberculosis may be dispensed with. Moreover, one is reluctant to persist in what may be an unnecessary application of pneumothorax in cases of comparatively small children, for they dread the pain. Furthermore, accumulation of purulent fluid in the pleural cavity and other complications may make the condition worse rather than better.

No medication is, as a rule, required. Theoretically, calcium therapy may be justifiable. Cod liver oil in the usual doses seems to improve the general condition of infants during the winter; older children probably do not need it. The diet should be a normal one with a sufficient amount of vitamins.

With the treatment already described primary tuberculosis heals with only comparatively few exceptions; other cases may run a malignant course. The question may now arise: What eventually becomes of the healed or healing primary complex? Can it occasion any indisposition, and, if so, of what sort? In the first place it may be considered how the healing primary complex appears pathologico-anatomically.

In speaking of fresh primary tuberculosis, I pointed out that the center of the pulmonary focus is necrosed with caseation to a greater or less extent. Together with the necrosing areas, productive changes begin to appear in the periphery of the focus. A wall of granulation tissue arises which tends to prevent the further progression of the primary tuberculosis. This tissue is composed of specific tuberculous changes with lymphoid, epithelioid and giant cells. Outside the granulation tissue there is finally a zone, more or less broad, of perifocal infiltration, histologically to be regarded as nonspecific. With the appearance of the zone of granulation tissue, the healing of the primary complex begins. As is known, healing proceeds by transformation of the structure of the lesion. Collagenous fibers begin to appear to an even greater extent in the granulation tissue; their cells die, and fibrils arrange themselves concentrically about the focus, contract and pack themselves together into a capsule of hyaline connective tissue.

In this stage of the development of the primary focus is found thus innermost in the core an area of caseous necrosis surrounded peripherally by connective tissue. If this were ordinary necrosis, e. g., as in an infarction of the kidney, the granulation tissue would grow into the dead parts, resorb and replace them and thus change the whole necrosis into a scar. The necrosis in the primary focus is, so to speak, active through the tubercle bacilli which lie there but are not yet dead. These bacilli prevent the necrosis from being replaced by connective tissue. The tubercle bacilli cannot, on the other hand, prevent the necrosis from undergoing another metamorphosis, namely calcification. Necrosis of this kind has a close affinity with calcium salts. The embedded lime first makes the necrosis doughy, then chalky and finally as hard as stone. It is in this last condition that one generally sees an old primary complex in the postmortem examination of children who have died of intercurrent diseases. The roentgenogram, as is known, reveals such a primary focus as a sharply defined, homogenous, dense shadow.

Primary tuberculosis consists, however, not only of the primary focus but also of tuberculous changes in the regional glands, and in the peribronchial and periarterial lymphatics that lie between the primary focus and the glandular lesions. When the wall of granulation tissue arises around the primary focus, there is also a wall of granulation tissue about the tuberculous foci of the lymphatics. The changes in tuberculous lymphangitis also continue to follow those in the primary

focus. When the lesion in the primary focus becomes a scar, those of the lymphatics follow suit, and certain small caseous parts involved by tuberculous lymphangitis may become calcified. When completely healed, there remains only an increase of the peribronchial connective tissue. In the roentgenogram the scar resulting from lymphangitis is visible in the form of an increase in density of the peribronchial tissue.

The same anatomic changes are also to be observed in the regional glands. In the healing of tuberculous lymphadenitis there is, as with the primary focus, a transformation of the connective tissue of the granulation type and a calcareous incrustation of the necrosis. Roentgenologically, in these cases the incrusted glandular lesions are seen as circumscribed, dense foci situated in the hilus.

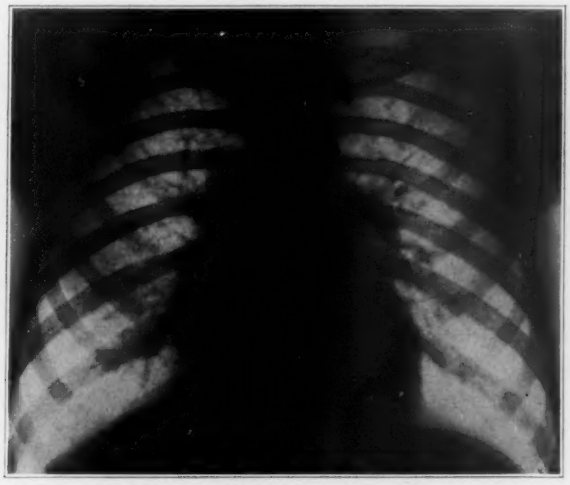

Fig. 10 (case 1).—Roentgenogram showing enlargement and densification of the hilus shadow on the right side, calciferous foci below in the same area of the lung and between the two areas increased connective tissue shown as lines and bands. These findings correspond to the primary focus, glandular lesions, tuberculous lymphangitis and the field of induration.

When primary tuberculosis has reached this stage of development, the remnant appears roentgenologically as a calciferous, rounded focus situated in the pulmonary parenchyma, one or several calciferous foci in the hilus of the same side and between the two foci an increased density of cords and lines, producing a greater increased density in this part of the area of the lung. The denser part, including the calcified foci, is called the field of induration (fig. 10).

If in the roentgenographic examination of a child with a positive reaction to tuberculin a calcified primary complex is found, the primary tuberculosis is generally regarded as unimportant so far as the health

of the child is concerned. The tuberculosis is looked on as clincally healed. Common experience has also taught the physician that he is justified in this opinion.

However, it must not be lost sight of that this healing is healing only in the clinical sense. Owing to the great resistance of the tubercle bacilli, they can remain alive and virulent in the calcified foci for many years. In fact, there have been primary foci many decades old which contained tubercle bacilli pathogenic for the guinea-pig. The lime is, of course, not a favorable field for the bacilli; their nutrition suffers from the constriction of the blood supply so that they finally die. Not until this has taken place can definite healing of primary tuberculosis be spoken of.

It is not known how often bacteriologic healing of primary tuberculosis takes place, and it is rarely that convincing proofs of biologic healing are reported. They can certainly be counted on the fingers of one hand. It is easy to understand that observations of this kind must be rare, since after such healing persons lose their sensitivity to tuberculin and, so far as one can judge, their specific immunity also and can, therefore, be freshly reinfected. In the great majority of cases the patient keeps his once acquired tuberculin allergy and thus retains the tubercle bacilli.

One may now wonder what becomes of the altered lesions already described. Do the once calcified foci remain through life as witness of what took place in childhood, or do they gradually disappear?

The fact that resorption of the lime of the primary complex may take place and the way in which it does so were anatomically shown in examinations made by the pathologist Bietzke. From the surrounding connective tissue small columns of vessels and cellular connective tissue grow into the lime and cause its resorption. When the process is finished, either the whole focus is replaced by connective tissue or there may remain only a few spicules of lime.

My own clinical observations of the condition of the calcified primary complex support the notion that it may undergo considerable regressive changes, though as yet I have not had an opportunity of observing a patient long enough for the establishment of the complete disappearance of a calcified focus. The roentgenologic reduction of a calcified primary focus is, as a matter of fact, seen not at all rarely. As examples of such regression the following cases are cited:

CASE 1.—Ingrid Z., a girl aged 4 years, was admitted to the Children's Hospital for treatment of fresh primary tuberculosis. When, after two years the process of calcification had become clear and had marked off the primary focus from the surrounding perifocal infiltration, the focus was as large as a hazelnut, and the lime was distributed in the form of a mulberry. At this time the glandular lesions did not yet appear calcified. Not until a year later, when the roentgenogram was taken, did the calcareous incrustations become noticeable even in the glands and

mark off a focus as large as a full-sized hazelnut. At the same time calcification of the primary focus was more distinct. After another two years, the primary focus was scarcely as large as a pea, and the glandular focus corresponded in size to about that of a brown bean. At the end of nine years more, the primary focus was no larger than a grain of rice and the glandular focus than a pea. There can be scarcely a doubt, in my opinion, that the lime will gradually be resorbed altogether, so that in the course of, perhaps, another five or ten years, one can

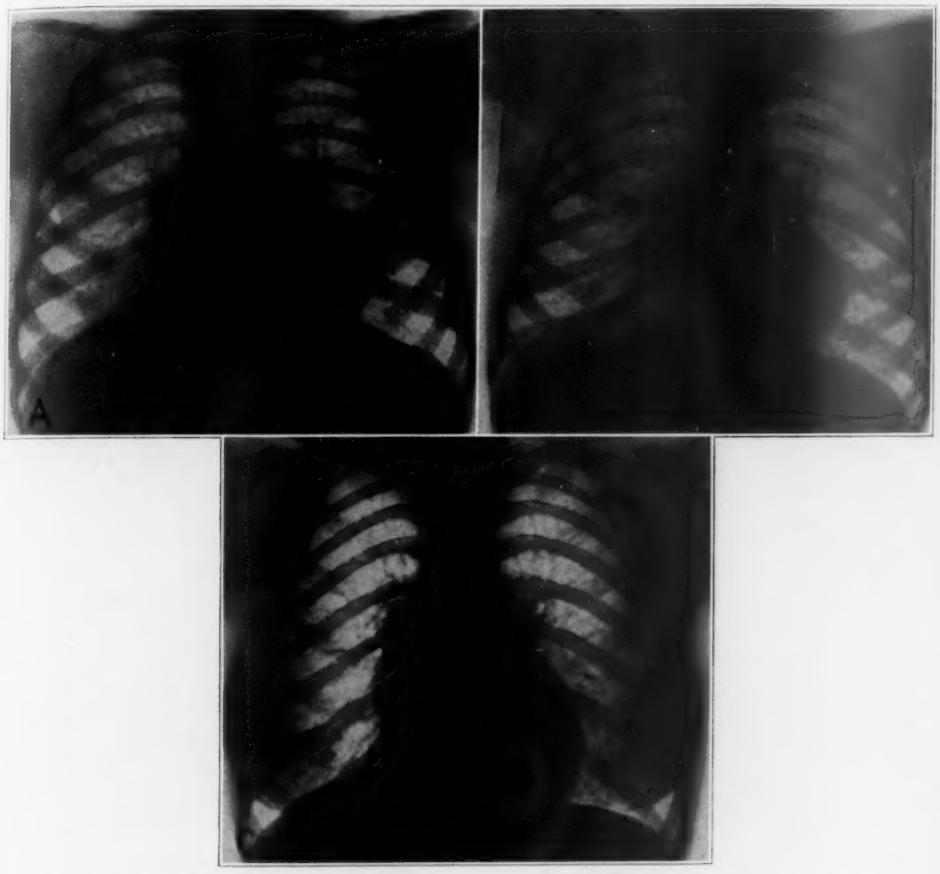

Fig. 11.—Roentgenograms of Ingrid Z. *A* shows the size of the calcified primary focus in the supradiaphragmatic part of the right lung; *B*, the diminution in the size of the calcified primary focus shown in *A* two years later; *C*, the size and appearance of the calcified primary focus seen in *A* and *B* eleven years after the manifestation of primary tuberculosis.

no longer determine from the roentgenogram with any degree of exactitude where the primary focus was situated (fig. 11).

Case 2.—Erik A., a boy aged 7 years, the roentgenogram of whose chest was taken in 1924, had at that time fresh primary tuberculosis which involved the middle two thirds of the pulmonary area on the left side. A year later the calcifi-

cation of the focus, shown in the figures, had begun, and the calcified area was about as large as a plum. Two years later, the size had diminished by about one-third, and the denseness had greatly increased. In 1933, the ninth year after the disease began, the area of calcified primary tuberculosis was only about one quarter of that it occupied when calcification began (fig. 12).

The reduction in size that the calcified foci have undergone in these two cases during the last ten years is evidently most pronounced. The

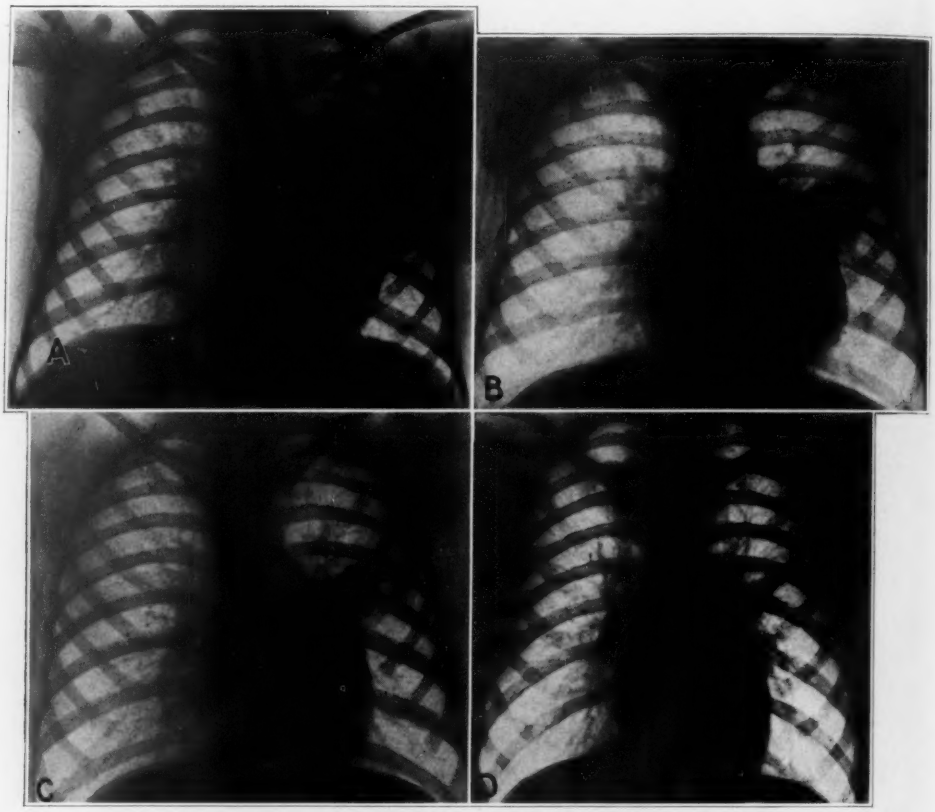

Fig. 12 (case 2).—Roentgenograms of Erick A. *A* shows the aspect of the perifocal infiltration at the time of the manifestation of primary tuberculosis; *B*, the beginning of calcification of the primary focus of tuberculosis shown in *A*; *C*, the marked diminution in the size of the calcified primary focus shown in *B*; *D*, taken in 1933, a marked diminution in the calcified primary focus.

roentgenologically evident reduction of the foci must correspond to an anatomic reduction, since the decrease in size cannot be explained as a roentgenologic misinterpretation.

The most striking impression of the changes in the calcified foci which are produced in the course of years may be obtained if the

silhouettes of the different roentgen shadows are compared. In the first case the calcified shadow has decreased in nine years to one tenth of its original size, and in the other case it has decreased to about one fifth (fig. 13).

The calcified foci do not merely decrease in size. They grow denser and denser. This increase in density, as well as the decrease in area

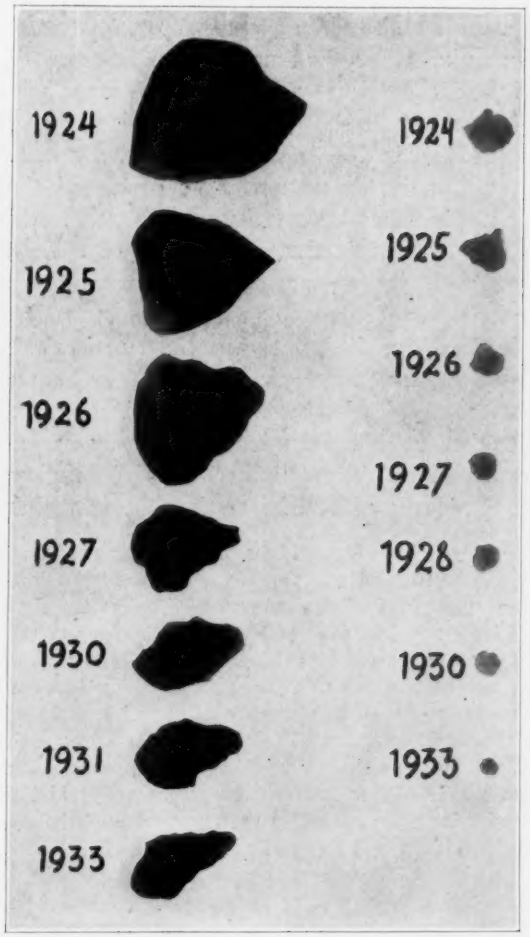

Fig. 13.—Silhouettes of the roentgen shadows of the primary foci in cases 1 and 2 of primary tuberculosis, showing the gradual diminution in the size of these calcified foci.

must, of course, be due to the compression of the calcium salts through the contraction of the capsule of connective tissue, and to the intensification of the calcareous incrustations. In this way, therefore, from a large and noncompact shadow an unpretentious, rounded and rather

dense focus, or, in other words, a projectile shadow of the type seen in closure of the semilunar valves is gradually obtained. This will probably be true of the calcareous focus in case 2 after the lapse of another ten years. It may be that many of these hazelnut-sized, sharply defined, round shadows that can occasionally be seen in the middle of the pulmonary area in adults or older children once consisted of a comparatively large lesion primary of tuberculosis, as in case 2.

A similar accentuation of the calcareous density does not, however, proceed continuously. When the lime begins to be resorbed, as in case 1, the density of the focus decreases in its turn, the lime being, as it were, split up, and the roentgen shadow becomes thinner, so that it is not difficult to imagine that in time it may disappear altogether.

Nevertheless, it must by no means be concluded that all foci of primary tuberculosis leave behind them calcification when they heal, with resultant roentgenologic traces. They do not. In fact, not even extensive, roentgenologically demonstrable primary tuberculous infiltrations necessarily leave behind them roentgenologically demonstrable calcifications in the lung. Before the possibility of calcification is precluded, several years must have elapsed, as it may take a long time in certain cases before calcification begins. This applies especially to infants, though, on the other hand, calcification is extremely frequent with them. As an illustration of noncalcareous healing of a primary focus which had given rise to a vast perifocal infiltration, the following case is cited.

CASE 3.—Roy P. was brought to the hospital at the age of 5 months with high fever, general poor health and a roentgenologically and physically demonstrable infiltration in the upper half of the pulmonary area on the right side. As the boy reacted positively to tuberculin and his general health was much affected, the process was diagnosed as caseous pneumonia. Unexpectedly, the condition improved; the temperature became normal after a week; the child gained weight, and about six months later the first signs of a decrease in the size of the infiltration were found in the roentgenogram. The physical signs progressively diminished, and after five years the large shadow had disappeared, except for a small remnant corresponding to the interlobar fissure between the upper and the middle lobe. At the last examination ten years after the appearance of the disease, there was a distinct area of calcification the size of a brown bean in the most medially situated gland of the hilus, while there was no trace whatever of calcification at the spot in which the infiltration, and presumably the original primary focus, had existed (fig. 14).

I now come to the important question of the significance of a healed primary complex from the point of view of the child's health. I have already mentioned the usual view that in such cases tuberculosis has ceased to affect the health of the child. This conception is based on the experience that from the time of healing the child does not generally show symptoms of illness that can be associated with tuberculosis. There are, however, exceptions, and important ones, and I shall therefore

deal with the phenomena that arise in connection with healed primary tuberculosis as seen roentgenologically. I shall omit such secondary complications as tuberculous meningitis and pleurisy and shall confine myself to the complications that are connected directly with the pulmonary foci of primary tuberculosis.

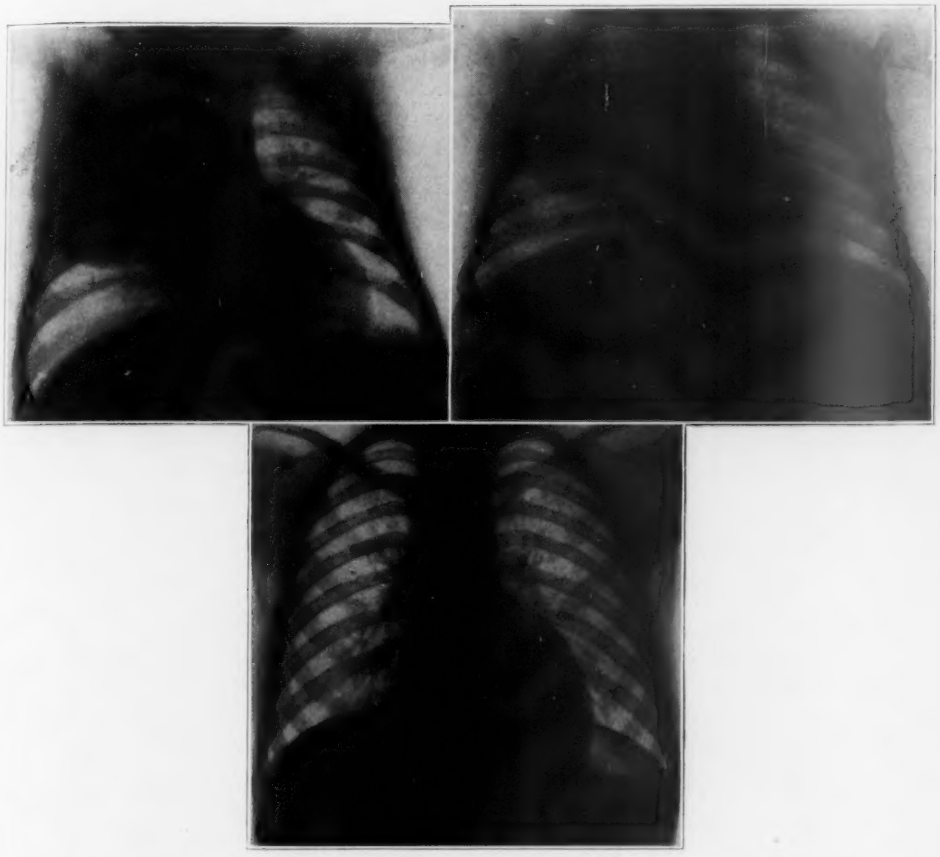

Fig. 14.—Roentgenograms of Roy P. *A* shows the large perifocal infiltration of the right lung; *B*, the beginning of the diminution of the large perifocal infiltration shown in *A*. In *C* taken eight years after the manifestation of primary tuberculosis, no calcified primary focus is to be seen; in the right hilus is a calcified glandular lesion.

The local symptoms of disease which may in exceptional cases arise in connection with roentgenologically demonstrable healed primary tuberculosis are of two widely different kinds: specific and nonspecific.

The specific complications that arise subsequent to, and in direct connection with, healed or healing primary tuberculosis consist, of course,

of tuberculous involvements. With respect to their course and appearance two kinds may be distinguished directly associated with an old primary complex in the lung. In each case it is a question of the specific tuberculous process becoming active again. In one case reactivation leads to the occurrence of the anatomic changes connected with healing as in the onset of primary tuberculosis; in the other, it leads to tertiary pulmonary tuberculosis. In these studies, however, I confine myself to primary tuberculosis and therefore do not enter on a description of tertiary pulmonary tuberculosis arising from an old primary complex. As an example of an exacerbation of primary tuberculosis during healing, the following case is cited.

CASE 4.—Harriet A., aged 14, in February 1931, two years prior to admission, had an attack of primary tuberculosis, with a temperature of 40 C. (104 F.). The roentgenogram then yielded the following evidence: A massive, homogeneous infiltration, the size of an almond, with diffuse limitation occurred in the right hilus. Laterally in the sceond interspace on the same side, there was homogeneous infiltration, about the size of a hazelnut, without decided sharp limits. The second shadow evidently corresponded to the primary focus. Tubercle bacilli were shown in the water from lavage of the stomach. Three weeks later the girl was free from fever, and when, after six months of treatment, she was discharged a pea-sized and fairly compact primary focus and a slight remnant of hilar infiltration were left. The girl remained well until October 1932, when she had an attack of high fever and coughing. The roentgenogram showed, in the second interspace on the right side, a fairly dense, homogeneous shadow with a denser part laterally in the same interspace, corresponding to the site of the earlier primary focus, and compact calcareous foci in the right hilus. No tubercle bacilli could be detected at that time. Two weeks later the girl was free from fever. It was fully a month later before there was a sign of the diminution of the infiltration, but the roentgenologic improvement continued, and when the patient was discharged from the hospital after six months the roentgenogram appeared about the same as before the new infiltration. Possibly some increase in traction might be noticed in the field of induration (fig. 15).

One may ask what caused the primary tuberculosis, which was healing well, to flare up again in this patient. Many investigators are of the opinion that exogenous reinfections produce such relapses. These exogenous reinfections are thought to act in about the same way as excessive injections of tuberculin and to show the result of a kind of focal reaction. In this case there had been no provable possibility of exogenous reinfection or any other provable factor that might have produced activity in the focus.

An important question is the value of the immunity bestowed by primary tuberculosis when persons with residual tuberculosis of this kind are subjected to a new attack of the disease. One must distinguish carefully between immunity as it manifests itself toward exogenous superinfections, particularly of a massive type, and immunity to the tubercle bacilli which the body already harbors and to which it has

reacted as an endogenous exacerbation. Persons having remnants of primary tuberculosis and manifesting sensitivity by a reaction to tuberculin possess a certain resistance to exogenous superinfection. The degree of this sensitivity is relative, and the immunity is variable but present. In cases in which the tubercle bacilli are latent in old tuberculous foci without being in contact with the body fluids, immunity, as indicated by sensitivity in such persons, may be ineffective. The

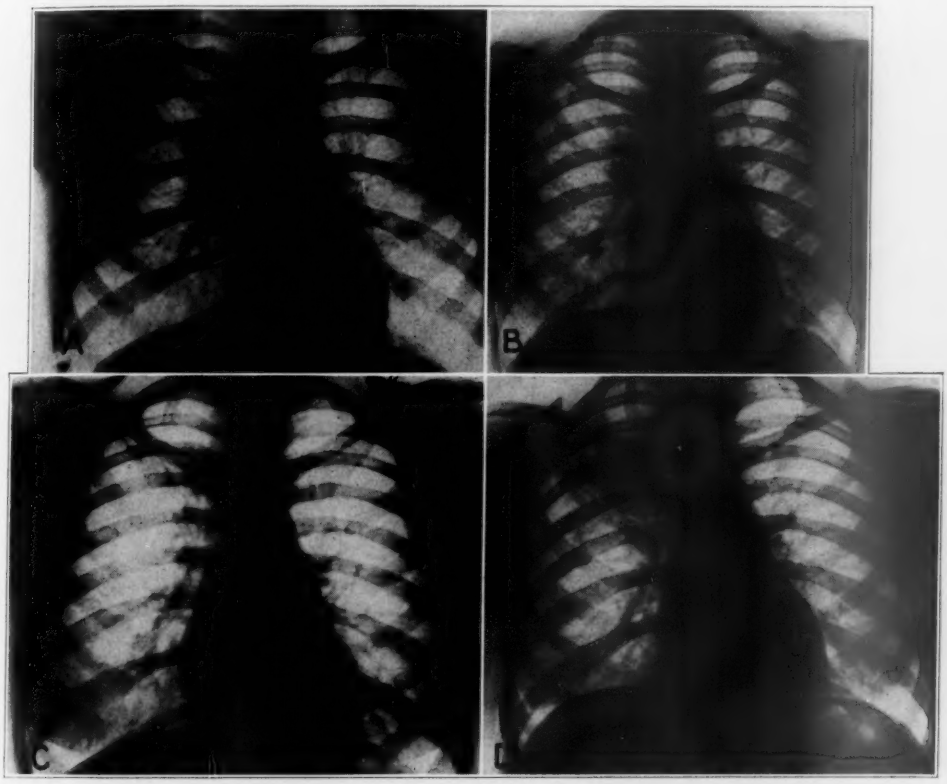

Fig. 15.—Roentgenograms of Harriet A. *A* shows fresh primary tuberculosis. In the second interspace laterally is seen the primary focus. The enlarged shadow in the hilus corresponds to glandular swelling. *B*, taken a year later, reveals marked diminution in the size of the perifocal reactions of the primary focus and of the glandular lesions. *C* was taken after the relapse and appearance of the new infiltration, localized in the field of induration. *D* was taken nine months after the manifestation of the relapse. The appearance is similar to that seen in *B*.

relative immunity conferred on the body in the development of sensitization through primary tuberculous infection is not an absolute protection against the organisms which have produced the primary disease. Pathologic processes extending from this primary infection may pro-

duce serious consequences, as is evidenced in early generalization of the infection following, for instance, the perforation of a caseous lymph node into a pulmonary vein or into the thoracic duct. More effective protection is apparently afforded in cases in which exogenous superinfections occur in the presence of immunity developed through the primary infection. It is as though the bacilli of the primary infection jealously defend themselves against the entrance of intruders, in order to hold sway in the organism which they have conquered. In most cases the powers of resistance of the child succeed in holding these latent tubercle bacilli at bay, but various causes may prevent the defensive powers of the organism from discharging their duty, and the field then lies open to the activity of the bacilli.

It must not, therefore, be imagined that primary tuberculosis on healing renders the child immune to secondary and tertiary forms of tuberculosis or to an activation of the old primary tuberculosis itself. Such relapses as that just mentioned are, however, seldom seen in a case of old primary tuberculosis. In cases of comparatively fresh primary tuberculosis they are more frequent and are usually brought about by a preceding acute infectious disease, such as measles, pertussis or a common cold. Hitherto, I have not seen that an exogenous reinfection has had this effect, but I will not, on the other hand, deny the possibility of such a pathogenesis.

As is well known, there are two opinions in regard to the effect of measles on primary tuberculosis. Some authors deny that measles has a serious effect on manifest primary tuberculosis, while others emphasize that tuberculosis often takes a malignant course after the child has had measles. I think that these differences in opinion may be explained by the stage of the primary tuberculosis when measles manifested itself. In fresh primary tuberculosis there are often relapses or exacerbations of the process after measles. On the other hand, in healing or calcified primary tuberculosis there is never or rarely a change for the worse under the influence of measles. What is said of measles may be said of all other acute febrile diseases; in cases of old primary tuberculosis there is no danger of activation; in cases of fresh primary tuberculosis there is now and then an exacerbation of the tuberculous process.

If consonant râles are found in a child over the same spot in which they were heard previously in a primary tuberculous process, it is usually concluded that the present stage of the disease is that of tertiary pulmonary tuberculosis. However, the physician must beware of concluding merely from physical signs that the lesion is pulmonary tuberculosis, even if he has previously cared for the child with primary tuberculosis of the same localization as that in which the changes were discovered. The substratum of the râles which, anatomically viewed, corresponds to catarrh in an indurated pulmonary parenchyma need

not be the expression of tertiary pulmonary tuberculosis. Not even an ordinary roentgenographic examination showing the presence of old tuberculous foci justifies one in the diagnosis of tertiary pulmonary tuberculosis. Contrary to what is true of adults, it is in fact comparatively rare for such physical and roentgenologic symptoms to be due to ordinary pulmonary tuberculosis. The illness that in children with an old primary complex usually causes these symptoms is, on the contrary, bronchiectasis. This brings one to the nonspecific diseases that follow clinically healed primary tuberculosis.

It has been common knowledge that bronchiectases can arise in connection with anatomic changes produced by a chronic tuberculous process in the lung. In necropsies performed on persons who have died of chronic pulmonary tuberculosis it is common to meet, along with cavities, other hollow formations that consist of dilated bronchi.

It is, however, not only tertiary pulmonary tuberculosis that, in healing, can give rise to bronchiectases. Generally speaking, all regressive tuberculous changes can cause such anatomic or functional lesions of the bronchi that bronchiectatic formation is favored. This is not least in the case of primary tuberculosis.

The most important cause of an acquired bronchiectasis is now held to be an injury to the bronchial wall, though one may admit the importance of the contraction of the surrounding connective tissue. The change in the bronchial wall consists of loss of the cilia, destruction of the epithelium and weakening of the musculature and elastic elements of the bronchus. Peribronchitic changes also contribute to the occurrence of the dilatation of the bronchi. Owing to these changes the bronchi are transformed into stiff tubes that lack the power of peristalsis and are deprived of mucous glands and normal epithelium. The anatomic changes need not be marked; the functional ones may be of more importance.

Such changes as I have described may be produced by primary tuberculosis on healing. That the mucous membrane of the bronchi may be damaged by the perifocal process surrounding them is easy to understand, as is also the fact that peribronchitic lymphangitis may leave a foundation for contraction of and traction on the bronchial passage.

These bronchiectases, which occur in connection with the healing of primary tuberculosis, have generally little influence on the health of the child, but knowledge of their existence is important when the anatomo-etiologic basis of the physical changes discovered must be judged. Bronchiectases are rather common, certainly commoner than true tertiary pulmonary tuberculosis following primary tuberculosis. The more one is on the lookout for these postepituberculous bronchiectases, the more often they will be found.

It is certain that in many cases bronchiectasis following healed primary tuberculosis have been mistaken for tertiary pulmonary tuberculosis. This is easy to understand, for there is always the temptation to interpret the disease as pulmonary tuberculosis when one is dealing with children reacting positively to tuberculin with roentgenologically visible foci and consonant râles localized in the same area. In a number of cases the conditions are still more deceptive when one is dealing with a child that has been previously treated for manifest primary tuberculosis localized in the area of the physical changes. That was true, for instance, in the case of the girl just cited.

CASE 5.—Ingrid Z., aged 4 years, was taken violently ill with fever on Aug. 13, 1922. After having fever for a week, she was admitted to the hospital and was then found to be suffering from fresh primary tuberculosis. There was a cloudy density between the heart and the diaphragm with diffuse limitation exteriorly. The only physical change was a slight tympany. The girl was soon free from fever. During the next few years the girl, for social reasons, was nursed periodically at the hospital. Her condition was good at all times, though the roentgenogram still revealed changes. It was not until a year after the onset of the disease that the infiltration became thinner laterally and yet another year before calcareous dense foci began to appear. Since then the disease has been under control, and the patient has not shown other symptoms of disease or objective changes than the calcified primary complex. At a school examination in 1930, eight years after the disease began, the patient had numerous constant râles low down in front after coughing. She was still free from symptoms. It was suspected, however, that the old primary tuberculosis had again become active; she was admitted to the hospital for observation. Her general condition was then excellent; she had no fever or cough. The result of the blood sedimentation test was normal. A physical examination revealed constant râles low down in front and on the right side without dulness. The roentgenogram revealed only the calcified primary complex. Contrast filling, tried in the bronchi of the lower lobe of each lung, showed that the tubes were dilated in the middle lobe and formed structures like clusters of grapes, consisting mostly of peppercorn-sized bags located pericardially (fig. 16).

The fact that contrast filling of the bronchi enables one to detect bronchiectasis in the indurated area need not, of course, rule out a possible tuberculous process at work in the same place. Contrast filling does not, therefore, suffice. It must always be supplemented by an examination for tubercle bacilli. As the patient did not cough, the sputum could not be examined. Lavage of the empty stomach yielded no tubercle bacilli in the water with which guinea-pigs were tested. The patient's subsequent condition rendered the idea of pulmonary tuberculosis untenable. Her condition remained excellent; the temperature and blood sedimentation rate were normal. The consonant râles still remained detectable over the same spot.

Similar cases in which bronchiectases arise after perifocal infiltration are not uncommon. Last year I had the opportunity of observing

7 cases. It has not always been possible to follow the disease through its entire development, but a calcified primary complex may indicate the antecedent to the stage of bronchiectasis.

As a rule, bronchiectases that arise in the field of induration can be treated as trifles. The children do not need treatment for this condition. On the other hand, if tubercle bacilli are found, that is, if there

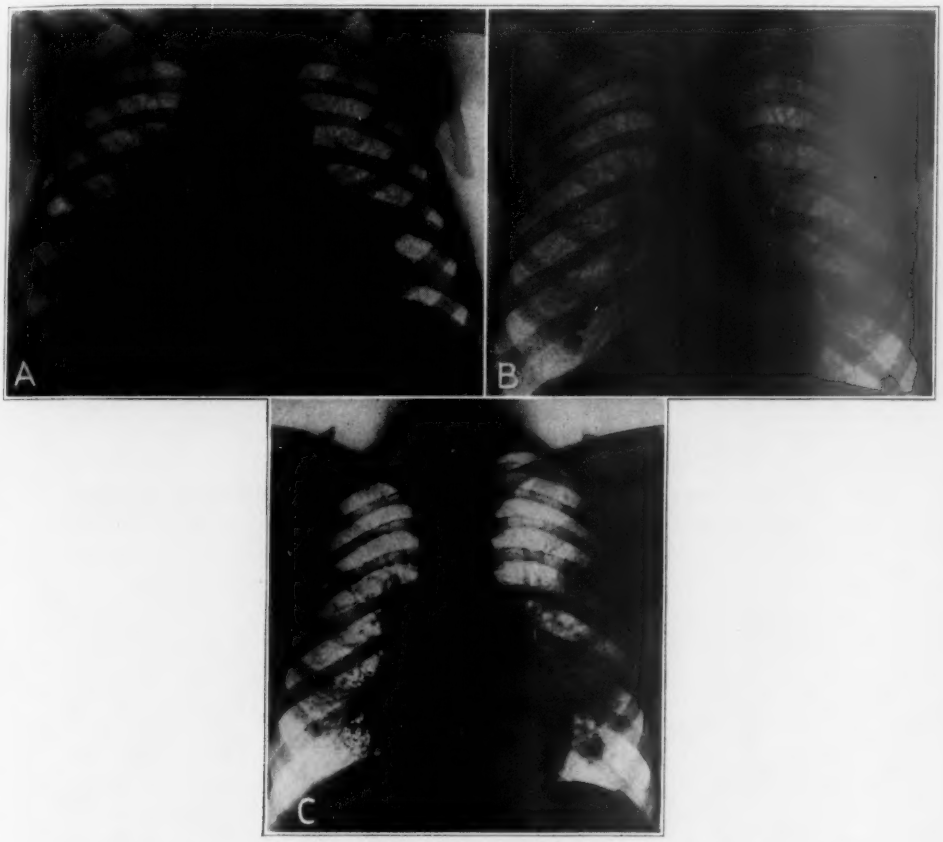

Fig. 16.—Roentgenograms of Ingrid Z. *A* shows the fresh primary tuberculous infiltration occupying the lower half of the area of the right lung; *B*, roentgenogram made when the physical symptoms of bronchiectasis were discovered; *C*, contrast filling of the bronchi at the place of a field of induration, showing bronchiectasis in the lower part of the right lung.

is in addition to bronchiectasis a true tuberculous disease, the case must be taken more seriously. Examples of such cases are found now and then. The existence of such complicated cases shows how important it is, in judging these types, to utilize all the sources at one's disposal in order to throw as much light as possible on the disease.

In certain cases, the contrast filling of the bronchi is rendered difficult, namely, in very small children and in patients in whom the apexes of the lungs are concerned. Then, of course, the suspicion of pulmonary tuberculosis is still greater, owing to the localization, and therefore the demonstration of bacilli is of still greater value. This also holds good in cases in which the contrast filling gives no definite support to the diagnosis of bronchiectasis. This situation is not rare. There may be constant râles in the area of induration, but in the examination of the bronchi contrast filling shows normal conditions. In these cases, one is probably dealing rather with a functional injury to the bronchi within the field of induration which favors collection and retention of the secretion. Tubercle bacilli are not demonstrable in such cases, which clinically are in perfect conformity with those in which bronchiectases are verifiable.

I have reviewed the diseases consequent to primary tuberculosis. I have been able to dwell only on those which are in more direct local connection with pulmonary primary tuberculosis and its changes. The part played by primary tuberculosis is not, of course, exhausted by the manifestations I have mentioned, for, indirectly, primary tuberculosis is the starting-point also for tuberculous diseases of a quite different nature, such as meningitis, pleurisy, miliary tuberculosis and last, but not least, tertiary pulmonary tuberculosis. All these tuberculous diseases are, however, connected with primary tuberculosis in a different way from those I have been considering, and for this reason I have regarded them as not belonging to the same group of diseases I have dealt with in these studies on primary pulmonary tuberculosis.

ATLANTO-AXIAL DISLOCATIONS

UNASSOCIATED WITH TRAUMA AND SECONDARY TO INFLAMMATORY FOCI IN THE NECK

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Atlanto-axial dislocations in the absence of trauma, disease of the bone or congenital anomalies,[1] although occurring almost exclusively in children, have received little attention from pediatricians. A search of the medical literature resulted in our finding records of twenty-two cases. In addition, we report two of our own, diagnosed clinically with roentgenographic confirmation. Since the dislocations occur as a complication of certain acute diseases of childhood, prophylaxis and early recognition are incumbent on the pediatrician. No mention is made of this condition in the pediatric literature except in one French publication.[2] The cases have been reported under various descriptive names, such as malum suboccipitale rheumaticum,[3] distention luxation of the atlanto-epistropheal joints,[4] *maladie de Grisel,*[5] *Drehungsverrenkung des Atlas,*[6] spontaneous hyperemic dislocation of the atlas[7] and nontraumatic atlanto-axial dislocation.[8]

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1. Roberts, S. M.: Congenital Absence of the Odontoid Process, Resulting in Dislocation of Atlas on Axis, J. Bone & Joint Surg. **15**:988, 1933.

2. Tedesco; Grisel; Desfosses, and Tassin: Deux nouveaux cas d'énucleation de l'atlas par torticolis nasopharyngien, Bull. Soc. de pédiat. de Paris **28**:252 (May) 1930.

3. Böger: Ein Fall von Malum suboccipitale rheumaticum, Arch. f. orthop. u. Unfall-Chir. **3**:97, 1903.

4. Wittek, Arnold: Ein Fall von Distensionsluxation im atlanto-epistropheal Gelenke, München. med. Wchnschr. **55**:1836, 1908.

5. Desfosses, P.: Un cas de maladie de Grisel: Torticolis nasopharyngien par subluxation de l'atlas, Presse méd. **38**:1179 (Aug. 30) 1930.

6. Sudeck, P.: Ueber Drehungsverrenkung des Atlas, Deutsche Ztschr. f. Chir. **183**:289, 1923.

7. Jones, R. W.: Spontaneous Hyperemic Dislocation of Atlas, Proc. Roy. Soc. Med. **25**:586, 1932.

8. Berkheiser, E. J., and Seidler, F.: Nontraumatic Dislocations of the Atlanto-Axial Joint, J. A. M. A. **96**:517 (Feb. 14) 1931.

Corner,[9] in 1907, and Wittkop,[10] in 1910, in exhaustive accounts of rotatory dislocations of the atlas mentioned no cases without a traumatic origin. In 1910, Black [11] stated that this dislocation does not occur without a rupture of the ligaments and that this cannot be accomplished without violence. Ely,[12] in 1911, reporting a case of this lesion in a boy of 13 in association with acute rheumatic fever, apparently did not appreciate the possibility of a nontraumatic origin and obtained nine months later the history of a fall.

Bell,[13] one hundred and one years ago, described the case of a man with a deep ulcer in the back of the throat, who sustained a dislocation of the atlas. Presumably the ulcer destroyed the transverse ligament of the atlas. The question of syphilitic disease of the bone arises, since the case was reported in the days before roentgenography. Like Greig,[14] we consider the report lacking in essential details.

Böger,[3] in 1903, reported a case of unilateral rotatory dislocation of the atlas in a 17 year old boy, occurring during the course of true rheumatic fever. He expressed the belief that the rheumatic disease of the joints of the occiput, atlas and axis loosened the ligaments and resulted in dislocation. He cited similar cases reported by Jäksch and by Coudray of luxation between the atlas and the axis in association with chronic rheumatism. Recently, Stammers and Frazer [15] reported a case of this type.

Wittek,[4] in 1908, described the case of a boy of 11 who had wryneck following periostitis of the jaw resulting from an infected tooth. This author attributed the luxation to overdistention of the ligaments due to metastatic effusion into the atlanto-axial joint. Wittek expressed the belief that the ligaments had not been torn and that the odontoid process had not slipped under the transverse ligament. He could find no analogous case in the literature.

Jacobs,[16] in 1918, reported a case in a 5 year old child with a febrile condition; he expressed the opinion, as did Wittek, that the dislocation was due to distention of the joint and relaxation of the ligaments as a result of toxins.

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9. Corner, E. M.: Rotary Dislocations of the Atlas, Ann. Surg. **45**:9, 1907.
10. Wittkop, C.: Zur Kenntnis der Luxation des Atlas, Leipzig, E. H. Lehmann, 1910.
11. Black, Carl E.: Dislocation of Atlas, Illinois M. J. **18**:473, 1910.
12. Ely, Arnold W.: Subluxation of Atlas, Ann. Surg. **54**:20, 1911.
13. Bell, cited by Greig.[14]
14. Greig, D. M.: Clinical Observations on the Surgical Pathology of Bone, Edinburgh, Oliver & Boyd, 1931.
15. Stammers, F. A. R., and Frazer, P.: Spontaneous Dislocation of Atlas, Lancet **2**:1203 (Nov. 25) 1933.
16. Jacobs, Charles: Atlas and Axis Luxation, Am. J. Orthop. Surg. **16**:357, 1918.

Swanberg [17] and R. A. Jones [18] each reported a case of dislocation following tonsillectomy. Swanberg's case occurred in a 22 year old soldier who was treated for wryneck at various hospitals and had had roentgenograms taken on six occasions before a correct diagnosis was made. Jones' case was that of a boy of 10 years. These authors suggested that the luxation was caused by a rupture of the transverse ligament.

Sudeck [6] reported two cases of rotatory dislocation of the atlas which after critical scrutiny we believe should be included as instances of spontaneous dislocation of the atlanto-axial joint. The author explained these dislocations as due, in the one case, to excessive passive rotation under narcosis and, in the other, to incoordinated reflex action. He pointed out that in rotatory dislocations there are three pathologic positions of the head which are partially compensated for by positions assumed by the cervical part of the spine; they are as follows: (1) anterior lowering of the head by lordosis of the cervical part of the spine, (2) rotation of the head by the rotation of the epistropheus and the rest of the cervical portion of the spine in the opposite direction and (3) lateral inclination of the head by scoliosis of the spine.

Sudeck also called attention to what he termed the epistropheal symptom, in which the spine of the axis in atlanto-axial dislocation is found displaced to that side of the midline to which the head is turned. The existence of this sign is borne out in one of our cases and is substantiated in the reports of cases we have studied in which notes are recorded on the findings in the neck on palpation.

Sudeck expressed the belief that in his second case the transverse ligament gave way and that therefore the odontoid process of the axis encroached on the spinal canal and endangered the cord. His notion that this ligament gave way because the axis of rotation was changed from the dens to one of the lateral joints with the continuation of the extraneous force is disputable.

Brinckmann,[19] like Sudeck, attributed this dislocation to an incoordinated reflex action in the case of a boy of 5 in which trauma was absent. No mention was made of an antecedent history of inflammatory focus in the neck.

Grisel,[20] in 1930, reported two cases in girls of 8 and 9, the condition occurring in conjunction with nasopharyngitis. He expressed the belief

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17. Swanberg, H.: Anterior Dislocation of Atlas Following Tonsillectomy, J. A. M. A. **72**:107 (Jan. 11) 1919.

18. Jones, Rocyn A.: Dislocation of Neck at Atlanto-Axial Joint, Proc. Roy. Soc. Med. **26**:136, 1932.

19. Brinckmann, Erich: Die Drehungsverrenkung des Atlas, Klin. Wchnschr. **7**:649, 1928.

20. Grisel, P.: Enucléation de l'atlas et torticolis nasopharyngien, Presse méd. **38**:50 (Jan. 11) 1930.

that luxation was due to a spasm of the prevertebral muscles. He commented, as did Sudeck, on compensatory scoliosis. Desfosses, six months later, designated the condition as *maladie de Grisel* and described its occurrence in a girl of 7 following nasopharyngitis. The report by Tedesco, Grisel, Desfosses and Tassin [2] was the only one found in a pediatric journal. It summarized the two reports just mentioned and again stressed the part played by spasm of the prevertebral muscles. These authors reported a case following an operation on the mastoid in a girl of 12, and Fitzsimmons [21] reported a similar case in a girl of 11.

Berkheiser and Seidler reported five cases of atlanto-axial dislocation of nontraumatic origin resulting as a complication of acute rheumatic fever, scarlet fever, tonsillitis, influenza and acute coryza, respectively. They pointed out that anterior dislocations predominate because the center of gravity of the head is located farther forward than the anatomic support. They further stressed the fact that any other factor producing flexion of the head on the neck, such as recumbency with pillows under the head, also predisposes to forward dislocation.

R. W. Jones, in 1932, in reporting two cases of his own and twelve from the literature, emphasized the rarity of the condition and the absence of a traumatic factor. He stressed the occurrence of an inflammatory focus in the upper part of the neck as the one constant predisposing cause. This author designated his cases as those of spontaneous hyperemic dislocation of the atlas. In one of his cases, the roentgenogram showed marked decalcification of the anterior arch of the atlas but no destruction.

COMMENT

Since the anatomic relations, roentgenologic considerations [22] and treatment of atlanto-axial dislocation have heretofore received sufficient attention, we shall discuss only those topics which require further emphasis and clarification.

Pathogenesis.—As the exact mechanism concerned with the production of atlanto-axial dislocation is not known, several explanations have been advanced. Wittek presumed that it was due to an effusion into the joints with relaxation of the ligaments following an inflammatory focus in a nearby area. Jacobs stressed this possibility and cited the analogous occurrence of spontaneous dislocation of the hip in typhoid.

Hollenbach [23] called attention to the almost exclusive occurrence in children of spontaneous dislocation of the hip during the course of

21. Fitzsimmons, Henry J.: Four Cases of Unilateral Rotary Displacement of the Cervical Spine, Interstate M. J. **22**:983, 1915.

22. George, A. W.: A Method for More Accurate Study of Injuries to Atlas and Axis, Boston M. & S. J. **181**:395, 1919.

23. Hollenbach, J.: Die Spontanluxation der Hüfte im Verlauf von Infektionskrankheiten im jugendlichlen Alter, Deutsche Ztschr. f. Chir. **237**:441, 1932.

acute infectious diseases. He demonstrated by serial roentgenographic studies distention and subsequent dislocation in this joint. While objective evidence of distention of the atlanto-axial joint cannot be adduced, that spontaneous dislocation can, nevertheless, occur in this joint when the ligaments are weakened is suggested by the following observation:

Baudonin [24] discovered bilateral rotatory dislocation in a skeleton in which the odontoid process was not broken and attributed the condition to postmortem change. He thought that the dislocation had been brought about by the head's turning with its own weight after decomposition had weakened and loosened the ligaments and muscles. Greig also emphasized that neither the transverse nor any other ligament need be ruptured to allow vertebral displacement.

Decalcification as a result of hyperemia of the upper cervical vertebrae secondary to inflammatory processes in and about the pharynx was emphasized by Greig. When the bones are sufficiently decalcified, the slightest movement, perhaps merely the attempt to sit up, may bring about subluxation. This tendency is particularly marked in children because of the increased vascularity of the bones and the less firmly attached ligaments.

In the cases reported by Jones and Desfosses, decalcification of the atlas was demonstrated by roentgenograms, although Desfosses did not attach particular significance to it. On the other hand, Jones, in explaining the cause of this dislocation, stated that the degree of decalcification was such that the arch of the atlas no longer afforded secure attachment for the transverse ligament and with slight movement of the head the ligament was avulsed.

Grisel emphasized as a causative factor spasm and contraction of the prevertebral muscles, associated with lymphatic infection of the retropharyngeal space secondary to inflammatory conditions of the nasopharynx. That spasm of the muscles of the neck, and especially of the sternocleidomastoid, is frequent and occurs simultaneously with cervical adenitis resulting from infections of the nose, throat and ears was pointed out by Felix and Lüdecke [25] and also by Gillette.[26] This spasm, which often results in wryneck, was termed by the first two authors *lymphogener Schiefhals*. Treatment of the primary focus usually causes disappearance of the wryneck. This was demonstrated in the recent report of Piotet [27] of the case of a girl of 8, in whom torticollis

24. Baudonin: Compt. rend. Acad. d. sc. **189**:494, 1904; cited by Corner.[9]

25. Felix, W., and Lüdecke, E.: Der lymphogene Schiefhals, Ztschr. f. orthop. Chir. **50**:329 (Oct. 19) 1928.

26. Gillette, W. J.: Torticollis Due to Adenoid Vegetations and Chronic Hypertrophy of the Tonsils, New York M. J. **64**:158, 1896.

27. Piotet: Rare Complication in Removal of Adenoids: Case of Nasopharyngeal Torticollis, Schweiz. med. Wchnschr. **64**:355 (April 21) 1934; abstr., J. A. M. A. **102**:2070 (June 16) 1934.

following adenoidectomy, not dependent on luxation of the atlas, was relieved by treatment of a hitherto undisclosed complicating small retropharyngeal abscess.

Felix and Lüdecke reported persistence of torticollis as a not infrequent complication in these cases. They attributed this fixed wry position of the head caused by spasm of the muscles to arthritis of the cervical portion of the spine. In the latter instances, roentgenograms showed nothing significant, but the authors did not consider atlanto-axial dislocation in the differential diagnosis. The ease with which this diagnosis is missed even by roentgenography and the importance of pictures taken through the mouth should be borne in mind. Grisel, interestingly, commented on the fact that cases of atlanto-axial dislocation may often be reported as instances of cervical arthritis.

In our opinion, the production of atlanto-axial dislocation involves a combination of factors, the sine qua non being weakening of the lateral ligaments. Spasm of the cervical muscles in association with loose ligaments is a feasible mechanism. Nevertheless, it appears more likely that the dominant rôle played by the spasm is the prevention of spontaneous and easy reposition, with resulting locking of the overlapping edges. *Verhakung* is facilitated by the prominent edges of the surfaces of the joints (Wittkop).

In addition to the loosening of the lateral ligaments, other factors may play a rôle, for instance, rotation, particularly of an excessive nature. This was witnessed in Sudeck's own daughter when the head of the child was overly rotated during narcosis in exposing the abscessed cervical glands preparatory to incision. In the cases of Desfosses and Fitzsimmons following mastoidectomy and in our own case, the direction of the rotation corresponded to the side to which the head would be turned in exposing the field for surgical treatment.

Another immediate cause may be the fixed rotation of the neck assumed in the treatment of suppurative lesions of the neck. This, we believe, is a more plausible explanation in Sudeck's second case than that of sudden incoordinated reflex action, which, it seems to us, came as an afterthought to the author. We think that he did not conceive of nontraumatic dislocation in association with the infected burn of the neck. However, Wittkop described the case of a youth of 17 who sustained a dislocation of the atlas when he suddenly twisted his head to avoid being hit by a falling brick. No mention was made of a previous illness or of an inflammatory focus in the neck. This is a possible substantiation of the theory that an incoordinated reflex action, such as that produced by a sudden jerk of the head, can produce this lesion.

Injuries of the Spinal Cord.—We found no record of an injury of the spinal cord or of symptoms which could be attributed to such

a lesion in cases of atlanto-axial dislocations of nontraumatic origin with one questionable exception, the case of W. O. Reid, quoted by Greig.[14] This seems remarkable, especially since lateral view roentgenograms of the upper portion of the cervical part of the spine in the reported cases appear to show marked anterior displacement of the atlas and encroachment on the cord by the odontoid process of the axis. Bezi,[28] commenting on Berkheiser and Seidler's report, expressed surprise that no signs of compression of the spinal cord were mentioned.

Analysis indicates that there is a forward dislocation on one side only, and it is possible that the view of the projecting lateral mass is interpreted as the entire anterior arch of the atlas. In all readable plates of reported dislocations the anteroposterior view with the mouth open shows an overlapping of only one lateral articular facet.

The conception just stated is consistent with the idea that all dislocations are rotatory and that the odontoid process serves as the axis of rotation. This coincides with the view of the integrity of the transverse ligament. Sudeck was of the opinion that the odontoid process served as the axis for a certain degree of rotation and then moved laterad to one of the lateral articulations with further rotation. According to this view, shared by Berkheiser and Seidler, further rotation would lead to rupture of the transverse ligament. This, however, is not consistent with the facts pointing to freedom from injury of the cord and the normal physiologic action of the atlanto-axial joint.

Corner,[29] in discussing the physiologic action of this joint, indicated that two essential movements of the atlas take place, one with the odontoid process as the pivotal point (centric), the other with one of the lateral joints as the axis (eccentric). The eccentric motion is the more important and is especially used in slight rotation. When the degree of rotation is increased, centric movement around the dens as a pivot obtains. Hence, any strain due to overrotation falls on the lateral ligaments and not on the transverse ligament. Furthermore, Wittkop cited the experimental work of Uhde, indicating that great narrowing of the spinal canal with pressure on the cord occurs only when the pivotal point of rotation is lateral to the odontoid process of the axis.

The infrequency of injury of the cord in cases of unilateral rotatory dislocation due to trauma unassociated with fracture is consistent with the rarity of its occurrence in nontraumatic dislocation. Corner was able to find but one case of rotatory dislocation due to trauma uncomplicated by other injury in which the postmortem examination showed involvement of the spinal cord.

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28. Bezi, I.: Assimilation of Atlas and Compression of Medulla, Arch. Path. **12**:333 (Sept.) 1931.

29. Corner, E. M.: The Physiology of the Lateral Atlanto-Axial Joints, J. Anat. & Physiol. **41**:149, 1907.

REPORT OF CASES

Case 1.—P. G., a boy of 6 years, entered the institution with which we are associated for the first time on Oct. 27, 1933, with the chief complaint of stiffness and pain in the neck of four months' duration.

The parents, each aged 43, as well as two other children, aged 15 and 3 years, were living and well. There was no history of tuberculosis in the family or of exposure to that disease. The patient was spontaneously delivered at full term and weighed 7¾ pounds (3,615.3 Gm.) at birth. His infancy was uneventful; in early childhood he had pertussis, chickenpox and measles.

In June 1933 he had scarlet fever, which was followed by marked swelling of the glands on the left side of the neck. The glands suppurated and were incised under local anesthesia. They drained for about two weeks, during which period

Fig. 1 (case 1).—*A* is a photograph of the patient showing slight inclination of the head to the left and turning of the chin to the right; *B*, a lateral view showing a prominence to the right of the midline at the back of the neck.

the child complained of severe pain in the back of the neck, in addition to the discomfort caused by the swelling.

The head had been kept turned to the right during the time the glands were swollen and draining. It was soon discovered that the head could not be rotated back to the midline and that the pain in the back of the neck was increased with any movement of the body. The child frequently supported his head with his hands when sitting up, since he found that this position relieved the discomfort. The mother noted that the child snored while asleep and had difficulty in opening the mouth. This disability imparted a nasal twang to his speech.

Massage and passive motion were advised in an attempt to limber up the neck, since roentgenograms taken in July were interpreted as showing no pathologic condition of the bone. Roentgenograms were again obtained in September 1933 and

again interpreted as showing nothing significant. The father was urged to persist in his efforts to bring the head back in position by means of physical measures. After several weeks of patient waiting for improvement in the child's condition, the parents were convinced that something else than mere stiffness of the muscles was wrong and they therefore sought further help.

Examination at the time of admission revealed an ambulatory and well nourished boy, with a head of normal size. The ears, eyes and nose were normal. The lower jaw protruded. The examination of the throat was not satisfactory, since the mouth could not be opened fully. Palpation of the nasopharynx for the protruding lateral mass of the atlas mentioned by most writers was consequently not done. The head was inclined slightly toward the left shoulder and the chin was turned somewhat to the right. Active and passive rotation were not possible toward the left, although a small amount of rotation was possible to the right. Furthermore, there seemed to be impairment of the ability to lower and raise the

Fig. 2 (case 1).—Roentgenogram showing rotatory atlanto-axial dislocation secondary to inflammatory foci.

head along the horizontal axis. The right infra-occipital muscles were spastic, but no change was noted in the sternocleidomastoids. A bony prominence was felt to the right of the midline, which was interpreted as the spine of the axis (Sudeck's epistropheal spine sign). The parents noted some improvement in the wry position under physical therapy, which is explained by the compensatory attitude of the cervical part of the spine, described in the text and emphasized by Sudeck and Grisel.

The examination of the chest, abdomen and extremities gave negative results. The genitals were normal, except for slight phimosis. There were no pathologic reflexes either in the upper or in the lower extremities.

The laboratory examination revealed a faint trace of albumin in the urine, a negative reaction to the Pirquet test and a normal hemoglobin content and white cell, red cell and differential count of the blood.

A clinical diagnosis of rotatory atlanto-axial dislocation secondary to an inflammatory focus in the neck was made, which was confirmed by the roentgenogram (fig. 2).

CASE 2.—E. P., a girl of 11 years, entered the institution in April 1932 because of inability to move the neck. The essential facts in this case are as follows: The girl was well until five weeks prior to admission, when she contracted a cold, and one week following this acute infection, a stiff neck with inability to turn the head resulted. At first, pain was associated with the wryneck, being worse at night

Fig. 3 (case 2).—Roentgenogram showing atlanto-axial dislocation of nontraumatic origin.

and resulting in sleeplessness. It was impossible to open the mouth wide; fulness was felt in the back of the neck, and the head was turned to one side.

A clinical diagnosis of atlanto-axial dislocation of nontraumatic origin was made, and this was confirmed by the roentgenogram (fig. 3).

CONCLUSIONS

The known literature relative to atlanto-axial dislocation unassociated with trauma is reviewed.

The various conflicting opinions on the mechanism of the production of this lesion are presented.

The absence of injury to the spinal cord is discussed.

Two of our own cases recognized clinically with confirmation by roentgenogram are added to the twenty-two cases already reported.

Prophylaxis is suggested by the following means: (*a*) the early recognition of the condition by cognizance of its occurrence; (*b*) avoidance of overrotation of the head in exposing operative fields, as in operations on the mastoid and for suppurating glands, and (*c*) guarding against turning of the head in children with suppurative foci of the neck, necessitating the wearing of abundant dressings requiring frequent changes.

1819 West Polk Street.

ERUPTIVE FEVER WITH STOMATITIS AND OPHTHALMIA

ATYPICAL ERYTHEMA EXUDATIVUM MULTIFORME (STEVENS-JOHNSON)

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Stevens and Johnson [1] in 1922 reported two cases of "A New Eruptive Fever Associated with Stomatitis and Ophthalmia" in children. They could find no description of a similar cutaneous eruption and thought that no known diagnosis could be made from the symptoms and course of the disease. The eruption was generalized and presented well defined characteristics. It was first noted on the back of the neck and chest, and spread to the face, arms and legs during a period of eighteen days. When they first appeared the lesions were dark red, oval macules, varying from 0.5 to 2 cm. in the longest diameter and were without areolae. Within a few days these macules became papular and brownish purple. Some of the larger lesions acquired yellow, dry, necrotic centers. Vesicles and pustules were absent. Subjective symptoms of pain or itching were strikingly absent.

There were no lesions on the scalp, but the mucous membrane of the mouth was inflamed and eroded and bullae were noted in one case. The lips were swollen and crusted. During the third week, as the last lesions appeared on the palms and soles, resolution of the older lesions with crusting and scaling began. The latter feature was considered by the authors to be of diagnostic significance. Brownish, pigmented spots without pitting or scarring were seen at the sites of the healed lesions in the fifth week. The temperature fell with the onset of the period of resolution of the cutaneous lesions. The blood count in one case showed leukopenia on several examinations. In the second case, which was complicated by pneumonia, the blood count was not reported.

In both these cases purulent conjunctivitis with marked edema of the eyelids was an outstanding finding. In the first case healing was complete with a corneal scar remaining, but in the second case panophthalmitis developed and the patient became completely blind. A blood culture was made in one case and was found to be sterile. Bacte-

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1. Stevens, A. M., and Johnson, F. C.: A New Eruptive Fever Associated with Stomatitis and Ophthalmia, Am. J. Dis. Child. **24**:526 (Dec.) 1922.

riologic study of the discharges from the eyes, throat and lesions of the skin showed the usual pyogenic organisms.

One or both of these patients were seen by numerous experienced physicians, including Dr. Fordyce, Dr. Longcope and Dr. Emmet Holt, who found no recognized diagnosis which properly fitted this syndrome. Sepsis, pemphigus, erythema multiforme, a toxic eruption from either food or drugs, the usual exanthems and syphilis were considered and excluded by the clinical and laboratory findings. The authors thought that this syndrome of sudden onset with fever, conjunctivitis and cutaneous eruption was most likely that of an infectious disease of unknown etiology, and they expressed the belief that the condition deserved recognition as a clinical entity.

Fig. 1.—The patient in case 1 of Stevens and Johnson showing the extent and nature of the eruption on the thirteenth day of illness (from Stevens and Johnson [1]).

It is of interest in this connection that Dr. Stevens [2] has since learned that the patient in his first case had a recurrence of the rash shortly after his discharge from the hospital. The exact nature and duration of this eruption are unknown to him. He pointed out, however, that at the time of discharge there were still a few incompletely resolved lesions. One may therefore consider this a recurrence of the disease.

In 1929 Rutherford [3] presented a case of membranous conjunctivitis associated with a generalized eruption in a 27 month old child. The lesions were brownish-red maculopapules and were distributed on the forehead, cheeks, thorax and forearms. The rash persisted with varying

2. Stevens, A. M.: Personal communication to the author.

3. Rutherford, C. W.: Membranous Conjunctivitis with Loss of Eyeballs: Report of Cases, J. A. M. A. **93**:1779 (Dec. 7) 1929.

intensity for two months. The lesions extended to the scalp. Repeated cultures of the discharges from the eyes yielded the usual pyogenic organisms. There was a persistent purulent nasal discharge. Both eyes were ultimately enucleated. The patient was discharged after four months with pus still exuding from the sockets of the eyes. No comment as to the character of the buccal mucosa, the temperature reaction or the chronological development of the eruption is available.

There are several striking features about this case that are different from those already cited. These are the chronicity of the rash, the fluctuation in its intensity and the apparent absence of stomatitis. Rutherford, however, saw the patient on the sixtieth day following the onset. It is possible that a more complete history would have revealed lesions of the mouth. The fluctuations in the rash may be parallel to what seemed to be a recurrence in Stevens' first case. In the light of

Fig. 2.—The patient in Wheeler's case on the seventeenth day of illness showing marked swelling of the eyelids with profusion of pus, swelling of the lips with black crusts covering part of the upper lip and all of the lower and brown spots on the face and chest (from Wheeler [4]).

this case, Stevens' conception as to the short duration of the disease may have to be modified to include the possibility of recurrent efflorescences and a certain degree of chronicity.

Wheeler,[4] in 1929, reported a case that falls readily into the group under consideration. His patient was an 8 year old boy in whom general bodily pains and malaise developed, followed in two days by conjunctivitis. An eruption that looked like erythema multiforme except in its distribution appeared on the chest and back with a little on the extensor surfaces of the extremities. The buccal mucosa was markedly inflamed, and a grayish membrane was present on the lips, tongue and pharynx (fig. 2). Because of the severity of the ocular condition, the

4. Wheeler, J. M.: Destructive Purulent Ophthalmia Accompanying an Eruptive Fever with Stomatitis, Tr. Am. Acad. Ophth. **13**:508, 1930.

swelling and edema of the eyelids and the marked exudation of pus, the child was transferred to the ophthalmologic service of the Bellevue Hospital. Here Dr. Stevens recognized the similarity of the case to those he had reported. Although the protocol is not detailed, Wheeler pointed out that during the period of activity of the disease the temperature ranged between 98 and 101 F., most commonly near 100 F. This temperature was somewhat lower than that in the cases reported by Stevens. The lesions of the skin were eventually scattered over the entire body except the scalp. Formation of blebs did not occur. There were no subjective symptoms. The lesions healed with no disturbance of the distribution of pigment and without scarring. Bacteriologic studies gave uniformly negative results for diphtheria organisms and gonococci. Smears and cultures of the discharges showed a number of organisms, including Streptococcus, Staphylococcus and Micrococcus catarrhalis. Studies of the blood chemistry and urinalysis gave negative results. The blood count showed no increase in the total number of white cells, although polymorphonucleosis was noted. The Wassermann test was negative.

The patient left the hospital after seventy-nine days. In spite of treatment with irrigations of boric acid, hot and cold compresses, corrosive mercuric chloride and petrolatum, mild silver protein, atropine and ethylmorphine hydrochloride, the sight was completely lost in one eye and almost completely in the other. Wheeler pointed out that active treatment of the eyes is urgently indicated in cases of this type. In the hope of rendering more effective the treatment of the conjunctiva and cornea by irrigations and antiseptics, he advocated early canthotomy with thorough incision of the external canthal ligaments to release the eyeball.

Since publishing his original article in 1922, Stevens [2] has seen several other patients whose cases resemble those he reported. He has also had communications from several observers in this country and abroad in which similar cases were described. He has put his data at my disposal. Unfortunately, the protocols and studies in these cases are not sufficiently complete to record here. It must, nevertheless, be regarded as significant that other writers have found similar difficulty in classifying this peculiar syndrome with any recognized clinical entity.

It is more than likely that the literature contains numerous reports of this syndrome under other names, of which erythema exudativum multiforme (Hebra) is the most common. This term has been used to give dignity to a variety of incompletely understood eruptive fevers which were considered unusual or atypical varieties of the disease. Thus Smith [5] in 1929 reported such a case in a boy of 9 years who presented a

5. Smith, C. A.: An Unusual Case of Erythema Multiforme, Tr. Univ. Michigan Pediat. & Infect. Dis. Soc., 1929, p. 63.

diffuse bullous eruption involving the skin, mucous membranes and conjunctiva, with severe toxemia and high fever. Unfortunately, the child died of bronchopneumonia within six days after the onset. During the short course, however, the clinical features resembled those in the cases described by Stevens and Johnson.

Similarly, Bailey[6] in 1931 published three cases under the title "Lesions of the Cornea and Conjunctivae in Erythema Exudativum Multiforme (Hebra)." In these cases there was a generalized cutaneous eruption, associated with marked buccal and conjunctival involvement. One of the cases occurred in a person of 39. This patient was seen by Dr. Stevens, who thought that the clinical picture fitted in with that which he had described. The other two cases occurred in children, in whom, as in the first case, eventual corneal opacification and practically complete blindness resulted. These three patients were acutely ill, with high fever. Marked stomatitis was present. The ocular symptoms and sequelae were severe. Although the order of appearance and distribution of the eruption were not given in detail, the nature of the lesions and their course closely resembled those in the cases described by Stevens and Johnson. The desquamation emphasized by these authors was in Bailey's cases marked in the adult, absent in one child and not referred to in the other. One patient had a normal blood count; one showed a tendency to leukopenia, and the third had a leukocytosis, the white cell count being 16,000. The blood culture in these cases was sterile. Smears from the conjunctiva and mouth, when done (in one case), yielded Staphylococcus pyogenes-aureus.

Bailey recognized the resemblance of his cases to those already reported by Stevens and Johnson and included them, as well as the cases of Wheeler, Rutherford and numerous others (Fuchs, 1876; Molenes-Mahon, 1884; Gerke and Kain, 1892; Stark, 1918; Barkan, 1918; Hartler, 1921, and Raffin, 1922) in his review of the literature. He expressed the belief, however, that in these cases one is dealing with a rare type of erythema exudativum multiforme and not with a new clinical entity as suggested by Stevens and Johnson.

In December 1931 I had the opportunity of observing a case which, because of its similarity to those just described probably falls into the same category and is therefore worth reporting.

REPORT OF A CASE

History.—H. B., a Jewish boy 5½ years old, was admitted to the pediatric service of the Mount Sinai Hospital on Dec. 6, 1931. The child had been well until six days prior to his admission, when he complained of a general burning sensation over the surface of the body, malaise and extreme restlessness. He was

6. Bailey, J. H.: Lesions of the Cornea and Conjunctiva in Erythema Exudativum Multiforme (Hebra), Arch. Ophth. **6**:362 (Sept.) 1931.

taken to a physician, who found an erythematous, blotchy eruption over the upper half of the back. The nature of the eruption was not clear. The lesions were irregular in outline, varying in size from that of a pea to that of a walnut. The eruption persisted and spread; similar lesions appeared on the abdomen, the front of the chest, the face and the extremities, including the volar and dorsal surfaces of the hands and feet. The extensor and the flexor surfaces seemed equally involved.

The temperature was 102 F. and gradually rose to 104 F.

On the second day after the onset a profuse epistaxis occurred which was checked only after epinephrine gauze packing was applied. The mouth and lips early became red, painful and swollen. The child complained of pain on taking food into the mouth and on swallowing. On the third day after the onset the right eyelid became swollen, and on the fifth day the left eyelid became similarly involved. A profuse, thick, purulent discharge exuded from both eyes. The patient could open his eyes only with difficulty.

The cutaneous lesions from two to three days after their appearance were like small bullae. They ruptured spontaneously, with the escape of a clear brownish fluid. In the two days prior to admission to the hospital many of the lesions had faded somewhat, and the temperature had declined for a short period but had returned to 104 F. on the day before admission. Fleeting pains in the joints were noted; the joints, however, were not swollen or tender.

Blood in the stools, noted early in the illness, was attributed to the epistaxis.

There had been no headache, intestinal, respiratory or urinary symptoms. The patient had not been exposed to a similar illness, nor had he taken medication or eaten any unusual food.

The past history was essentially irrelevant. The boy had had the usual diseases of childhood, including pertussis two and one-half years before and measles one year before. No growing pains, pains in the joints or unusual eruptions of the skin had been experienced prior to this illness. There was no history of asthma, eczema or unusual sensitivity to food.

The family history was not significant. The father and mother had come from Russia many years before and were well. Two siblings were well. There was no familial history of allergic or rheumatic disturbances.

The persistence of the temperature at 104 F., the severe cutaneous eruption, the difficulty in taking food, the ocular symptoms and the failure to improve caused the parents to bring the child to the hospital.

Physical Examination.—Examination on admission revealed a fairly well nourished and well developed but acutely ill boy. He was mentally clear, although irritable and not cooperative. The temperature was 104 F.

A diffuse maculopapular eruption was noted on the face, chest, trunk and extremities. The lesions varied from the size of a pinhead to from 5 to 6 cm. in diameter. The border was irregular and frequently distinctly serpiginous, especially in the larger lesions. The smaller lesions were more common on the palms and soles and had the character of erythematohemorrhagic macules. The larger and older lesions, more numerous on the abdomen and chest, were definitely bullous in character and had a hemorrhagic base. The zone immediately around the bullous lesions was not inflamed. Some of the lesions were crusted and appeared as wrinkled, dry blebs on an erythematohemorrhagic base.

Marked fissuring, excoriation and edema of both lips were noted. The upper vermilion border was surmounted by a necrotic remnant of desquamated mucous membrane which protruded from the margin of the upper lip.

The eyes were swollen, and a profuse purulent discharge exuded. The cornea appeared to be free from involvement, although the surrounding conjunctivae were edematous and drawn into folds. A grayish pseudomembrane, which peeled off with difficulty, was present on the upper and lower lids on each side. The scleral conjunctivae were markedly injected in the areas in which the pseudomembrane was not present.

The scalp was free from lesions. A mucosanguineous discharge was present about the external nares.

The condition of the mouth was striking. The entire buccal mucosa was red, ulcerated in spots and covered with a whitish pseudomembrane which was friable and appeared like ruptured bullae. These lesions varied in size and were surrounded by a zone of marked congestion. The hard and soft palates were diffusely mottled and similarly covered with grayish-white patches. The tongue was not spared. It was reddened and swollen, and along its lateral aspect areas of ulceration covered by a grayish-white pseudomembrane were present. The gums appeared swollen and inflamed; considerable old and fresh blood was present along their margins, and numerous small grayish-white lesions were present. The posterior portion of the pharynx was only moderately congested; no ulcerative lesions were noted.

Except for the severe involvement of the skin and mucous membranes, the results of the physical examination were not striking. Adenopathy was generalized and included the axillary, inguinal, cervical and epitrochlear nodes; the enlargement, however, was only slight. The heart presented a soft blowing systolic murmur, which was heard over the apex and the base and which was thought to be functional. The lungs were clear. The liver and the spleen were not enlarged. Except for the stupor and irritability when the patient was disturbed, there were no significant neurologic findings.

Laboratory Data.—The hemoglobin on admission was 75 per cent (Sahli); the red blood cell count, 3,800,000; the white cell count, 6,800. The differential count showed: polymorphonuclear cells, 60 per cent, of which 10 per cent were nonsegmented forms; lymphocytes, 34 per cent; monocytes, 5 per cent, and eosinophils, 1 per cent. A second count showed 10,000 white cells, 85 per cent polymorphonuclears and 15 per cent lymphocytes. The bleeding time and coagulation time were normal.

Bacteriologic studies, including those of smears from the lesions of the skin and mucous membranes, were made at the various stages. From material from the punctured macular lesions, smears and cultures yielded no organisms. Smears of material from the bullae yielded gram-positive cocci, which on culture proved to be Staphylococcus albus. This organism was thought to be a contaminant of the skin. A smear of the exudate from the eye revealed numerous gram-positive diplococci, some with capsules suggesting pneumococci. No diphtheria or gram-negative organisms were found. On culture, Staphylococcus aureus was isolated. Smears and cultures of material from the nose yielded numerous organisms—the common inhabitants of the respiratory tract. Bacteriologic studies of the lesions of the buccal mucosa gave similarly unconvincing results. Numerous gram-positive organisms in short and long chains and in clusters were found. No organisms of diphtheria or Vincent's angina were found. A blood culture gave negative results.

The blood chemistry was within normal limits. The total cholesterol content was somewhat low—97 mg. per hundred cubic centimeters. The examination of the urine on admission and on subsequent occasions gave negative results except for an occasional white blood cell.

Course.—During the first three or four days after admission the patient was extremely toxic and stuporous. Dysphagia made the oral administration of fluids difficult and necessitated parenteral feeding. The child was given dextrose intravenously by the slow drip method almost continuously for the first two days, along with frequent retention enemas. The response to the forcing of fluids was rapid. The patient became more alert. He began to take fluids per os in small quantities, and by the end of the first week the oral intake was adequate.

The temperature, which was 104 F. at the time of admission, fluctuated between 101 and 102 F. for the first five days; the fever then became low grade for the next five days, after which the temperature dropped to normal.

The skin eruption, which was diffuse at the time of admission, increased in severity for the first three or four days thereafter. The lesions continued to appear on the trunk and extremities. More bullae became prominent, and at points where these broke the lesions became crusted. During the second and third weeks the older lesions on the chest and back began to scale, and gradually scaling occurred over the remainder of the trunk and the extremities. A violaceous pigmented area remained, marking the site of the lesion after the scales fell off (fig. 3).

Fig. 3.—My patient, H. B., during the third week of illness. The lesions were still marked, although resolution had begun.

The mouth was treated with frequent washings with sodium perborate and early began to show improvement. At the end of the first week, the buccal edema had markedly subsided; the ulcerative lesions had begun to heal, and the child was able to take fluids fairly well. Healing was not complete, however, until three or four weeks had elapsed.

The severe ulcerative and membranous conjunctivitis did not have such a fortunate course. Treatment with compresses, irrigations of saline solution and application of the usual antiseptic solutions and ointments was only partially successful. The left eye showed some improvement during the third week and gradually cleared, and normal vision was restored. The right eye, however, did not respond to treatment. As early as the second week the ophthalmologist, Dr. Robert Lambert, noted the development of purulent endophthalmitis. An anterior staphyloma then developed with an annular abscess about the periphery of the cornea. Because of the absence of visible corneal abrasion even on staining with fluorescein, the lesion in the eye was thought to be metastatic. The right eye rapidly became worse, the anterior staphyloma becoming more marked. It became irritable and chemosis was apparent. Dr. Lambert enucleated the eye during the

sixth week after the patient's admission. Histologic studies of the removed eyeball were of interest because microscopic abrasions of the cornea were found. Some observers considered these abrasions to be a possible portal of entry for the organisms producing the suppurative endophthalmitis, although direct extension through either the veins or the lymphatics was considered more likely. A metastatic origin of the ocular lesions was thought unlikely.

Except for suppurative otitis media of the right side, which developed during the third week and which slowly resolved, there were no other complications. The child was discharged from the hospital after a stay of eight weeks. The skin showed numerous pigmented spots; the mouth and the left eye were completely healed. The patient had gained in weight and was perfectly well.

The patient has been seen in the follow-up clinic four times within the year after his discharge. The pigmentation has considerably faded. An artificial eye has been properly fitted. The child has continued to gain in weight and is making excellent progress.

COMMENT

The unique resemblance of my case to those considered either as instances of the disease reported by Stevens and Johnson or as so-called atypical cases of erythema exudativum multiforme (Hebra) with involvement of the eyes and mucous membrane is striking. The slight variations in the nature and duration of the cutaneous lesions and the difference in the degree of buccal and ocular involvement should not prevent one from recognizing the identity of the more important clinical manifestations. Dermatologists [7] have frequently emphasized that the character of the cutaneous lesions is markedly altered by the degree of exudation. Thus, a certain eruptive fever that may cause macular or papular lesions in one patient may give rise to vesicular or bullous lesions in another. Of the cases considered, only in my case, in that of Smith and to a slight degree in one of Bailey's were there bullous lesions of the skin; in the others the cutaneous lesions were of the maculopapular variety. Similarly, the severity of the ocular manifestations, as has been pointed out by Rutherford, may simply be an expression of the degree of reaction. My patient presented a typical membranous conjunctivitis, as did that of Rutherford, whereas in some of the others the conjunctivitis was a severe purulent reaction without pseudomembrane.

In coming to the conclusion that the cases under consideration present a strikingly similar clinical picture and that my case belongs to this group, the possible variations in the severity of the cutaneous and ocular manifestations in an individual case were recognized. Here one is dealing with a group of cases that does not seem to fit into any known category. Bailey preferred to consider them rare cases of a known clinical entity (erythema exudativum multiforme, Hebra), while other investigators have preferred to group them as instances of a new clinical entity.

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7. Stelwagon, H. W., and Gaskill, H. K.: Treatise on Diseases of the Skin, ed. 9, Philadelphia, W. B. Saunders Company, 1923.

The accurate identification and establishing of a nomenclature for this condition is of course hindered by the failure to find a specific etiologic agent. In all the cases cited, no common predominating organism was found that might be incriminated. Furthermore, whenever blood cultures were made they gave uniformly negative results.

While specific evidence of the etiology is absent and no evidence of the contagious character of the disease has been obtained, I am inclined to believe with Stevens and others that the syndrome is the expression of a systemic infection. The marked febrile reaction, the severe constitutional symptoms and the eruption on the surfaces of the body and mucous membranes speak in favor of such a hypothesis. That numerous other conditions may be marked by fever and cutaneous eruption and may be associated with involvement of the conjunctiva and mucous membranes does not militate against this conception. The fact that drugs such as phenyl-ethyl-hydantoin can produce a similar reaction is well known.

In the final analysis, the diagnosis must be based on the clinical findings, which have been well summarized by Stevens as follows:

> Here is a syndrome of dramatic onset, with fever, conjunctivitis and cutaneous eruption. The child is prostrated, the mouth and tongue are inflamed and raw, the eyelids are swollen and pus streams from the eyes. There is a course of three or four weeks of high fever, with leukopenia. The eruption, unlike any hitherto described, comes out progressively for two weeks or more, matures, and resolves in horny crusts, in the order of its appearance. The temperature falls with this resolution of the skin lesions.

I should modify Stevens' conception of the course of the disease by the admission of the possibility of recurrent efflorescences over a longer period of time. In Stevens' first case and in Rutherford's, this occurred. The absence of definite leukopenia and the variations in the resolution of the cutaneous lesions need not contradict the diagnosis.

In the nine cases described in this paper, only two patients escaped total loss of vision, and even these two became partially blind. The severity of the ocular complications must therefore be emphasized. The possible involvement of the eyes and mucous membranes in erythema multiforme has frequently been referred to in the literature. More severe lesions of the type found in the group under consideration, however, have only rarely been stressed. Of the numerous dermatologic textbooks quoted by Bailey (those of von Hebra, Kaposi, Mracek, Crocker, Stelwagon, Schamberg, Darier, MacLeod and others), few emphasize the severity of these lesions. The question may therefore be raised as to whether these lesions represent unusually severe reactions in cases of erythema exudativum multiforme (Hebra) or whether they are part of another disease entity.

In his discussion Hanke [8] described a severe form of herpes iris conjunctivae with erythema exudativum multiforme in which the ocular lesions took on the characteristics of membranous conjunctivitis. In the severest cases, keratitis and corneal ulceration occurred. Dühring,[9] however, who reported one hundred and five cases of erythema multiforme (Hebra), described only a relatively mild conjunctivitis, which disappeared with the buccal lesions as the cutaneous eruption faded.

Present-day dermatologists do not, as a rule, associate severe involvement of the eyes and mucous membranes with the usual form of erythema exudativum multiforme (Hebra). When such severe lesions occur, the cases are termed atypical or rare cases of the disease. The cases of Stevens and Johnson, although strikingly similar to the so-called atypical cases of erythema exudativum multiforme (Hebra), were considered by the authors to constitute a separate entity. I am not certain that the differences are sufficiently striking to warrant such a separation. One finds, rather, sufficient resemblances in all these cases to think that they more probably belong to the same group. Although at present I do not consider myself justified in naming this group, I believe that if the condition is to be considered as an atypical form of erythema exudativum multiforme (Hebra) the name "Hebra" should be replaced by "Stevens-Johnson." This term would call attention to the unusual features of the condition emphasized by these authors. It would further serve to bring these variously designated conditions into one group. Whatever the title, it is hoped that such a conception will facilitate further study and investigation.

As to the pathogenesis of the ocular lesions which usually terminate in complete destruction of the eyeball or in severe scarring of the cornea, several theories have been advanced. That the lesions are metastatic in origin is to a considerable degree negated by the lack of evidence. One is rather inclined to the idea that they are the result of direct extension via the subconjunctival lymphatics or blood vessels or an extension of the superficial necrotizing, ulcerative process. The rôle of the secondary invader in this process is probably of marked importance.

The differentiation of the syndrome under consideration from various other eruptive fevers must take into account the variations in intensity of the multiple manifestations. The usual form of erythema exudativum multiforme (Hebra) is distinguished by its characteristic acute onset with multiform lesions on the extremities. Most commonly the lesions manifest a preference for the extensor surfaces and are symmetrical. The constitutional symptoms are comparatively slight, although

8. Hanke, V.: Der Herpes iris des Auges, Arch. f. Ophth. **52**:263, 1901.

9. Dühring, E.: Beitrag zur Lehre von den polymorphen Erythemen, Arch. f. Dermat. u. Syph. **35**:211, 1896.

occasionally they may be severe. The lesions may be macular, papular or vesicular. They heal without scaling and sequentially pass through a series of discolorations. There is generally absence of itching or marked subjective symptoms. A seasonal and an epidemic peak have been described. The relatively benign conjunctival and buccal involvement in the mild cases has already been commented on. The difficulties in the classification of the graver cases, in which involvement of the conjunctiva and mucous membranes may be severe, have been emphasized. As already indicated, this is the form of the disease of which I believe many cases can be chosen as identical with those described by Stevens and Johnson. In my case a diagnosis of erythema multiforme bullosum hemorrhagicum was at first strongly considered. Similarly, the first diagnosis suggested in Wheeler's case was erythema multiforme. It was only after the severe constitutional symptoms, the nature of the cutaneous lesions, the severity of the ocular symptoms and the marked involvement of the mucous membranes were appreciated, that the resemblance of my case to those described in the literature as atypical cases of erythema exudativum multiforme (Hebra) or as cases of a new clinical entity by Stevens and Johnson was recognized.

The differentiation of this syndrome from pemphigus must be made by the course and the nature of the lesions, which are bullous in character and lack multiformity. The ultimate outcome in the severe cases is death.

In cases of sepsis with multiple lesions of the skin, the history, the positive results of blood culture, the finding of a focus, the character of the individual lesions of the skin, the blood count, when possible, the rarity of ocular involvement and the course, help to establish the diagnosis.

A toxic eruption, due either to drugs or to food, may be ruled out—in the one case by the history and the course of the lesions; in the other, by the absence of severe gastro-intestinal symptoms.

Similarly, differentiation from the ordinary exanthems may be made by the history of exposure, the course of the disease and the evolution of the lesions. It is significant that Stevens' cases were early considered to be instances of severe measles.

From syphilis, the differentiation can be made by the history, the negative serologic reactions, the normal roentgenologic findings, the absence of the stigmas of syphilis and the course of the eruption.

From capillary toxicosis of the nature of that described by Frank [10] the condition may be differentiated by the absence of marked visceral manifestations, the negative results in tests of capillary fragility and the

10. Frank, E., in Schittenhelm, Alfred: Handbuch der Krankheiten des Blutes, Berlin, Julius Springer, 1925, vol. 2, p. 451.

failure to find red blood cells in the urine. The course of the lesions will help to establish the diagnosis. When lesions of the eyes and mucous membranes occur in this condition, they are less severe and differ in character.

As to the prognosis, one must not be misled by the insidious character of the ocular involvement. The ultimate visual impairment is so uniformly severe that too optimistic a prediction must be avoided. The effectiveness of the treatment used in my case, as well as of that used by others, is difficult to measure. When a patient comes to the hospital, his condition is usually severe. The suggestion of Wheeler, however, that early canthotomy may save eyes otherwise in danger of destruction, is worthy of consideration.

It is significant that heretofore these cases have been described in the main by the dermatologist and the ophthalmologist. A syndrome which seems to have its most striking incidence in childhood should fittingly be the subject of investigation by the pediatrician and the internist, and it is with the hope that others may be stimulated to recognize and record similar cases that this report is made. Perhaps more intensive clinical and laboratory studies of such cases early in the course of the disease may shed light on its nature, as well as on its more accurate classification and nomenclature.

SUMMARY

A case of an eruptive fever with cutaneous, buccal and ocular lesions similar to those in the two cases described by Stevens and Johnson as instances of a new clinical entity is here reported.

Similar cases described by Rutherford and by Wheeler are discussed.

The difficulty in classifying these five cases is considered.

The literature is reviewed, and the striking resemblance of these cases to certain others reported as instances of atypical erythema exudativum multiforme (Hebra) is pointed out.

The suggestion is made that all these strikingly similar cases be considered as belonging to one group. The exact classification and nomenclature of such a group are left open for further study and investigation.

If the term "erythema exudativum multiforme" is to be retained, it is suggested that the name "Stevens-Johnson" be substituted for "Hebra" in order to emphasize the unusual features of this disease.

A NEW DEVICE FOR FOOTPRINTING AND HEEL-PRINTING WITHOUT SOILING THE FEET

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In the daily use of King's [1] device in the office it became much more of a burden to clean the feet after the ink had been applied than to make the records. Therefore the problem arose of obtaining the same accuracy in recording without soiling the feet and heels of the child.

The device to be described and illustrated resembles in appearance that described by King [1] except that there is attached to the platform a rubber-covered double frame, hinged on the side, covering the strip of paper to be used for the record.

In the figure *A* depicts the device, which consists of a platform 6 feet (182 cm.) long and 14 inches (35.4 cm.) wide, built of ply wood. At one end is a roll of white wrapping paper, which may be either 9 or 12 inches (22.8 or 30.4 cm.) wide. The roll may be mounted so that the paper unrolls easily when pulled under the rubber-covered frame. I have found it convenient to have the roll and its supporting frame detachable for ease of handling. Hinged to the side of the platform is a frame 14 inches wide and 5 feet (152 cm.) long. Inside this frame is a second frame 13 inches (32.9 cm.) wide and 59 inches (180.3 cm.) long. This frame is cut 10 inches (25.4 cm.) from the end, and hinges are attached. Over the second frame is stretched firmly but not tightly a thin sheet of soft rubber (dental rubber dam). The second frame is then attached within the first by screws from underneath, so that the hinged end is left freely movable.

The double frame is attached to the platform bearing the roll of paper by hinges on the side. This allow it to be turned up for inking and for threading the paper. The under-surface of the rubber is inked with stamp-pad (with glycerin base) ink of any desired color by applying a roller covered with felt and saturated with ink. One inking usually lasts for several records, and the ink stays moist for many days. I have found it necessary to change the rubber covering about once every six months.

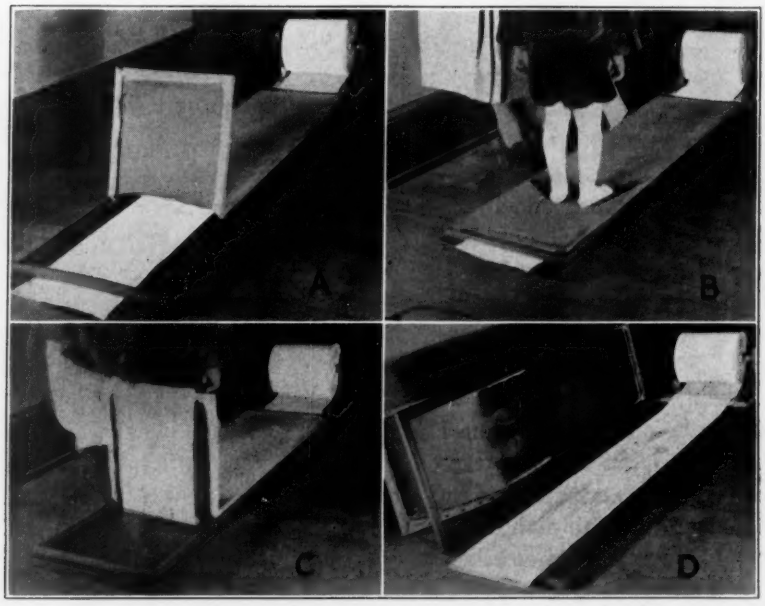
In *B* a child is shown standing on the rubber surface at the line of the hinges; *C* depicts the hinged end turned up against the heels and the strip of paper brought up against the inked surface so that pressure

1. King, Helen: A New Method of Recording Children's Foot Prints, Am. J. Dis. Child. **43**:89 (Jan.) 1932.

from a roller may record the heelprints. In *D* the double frame is turned back and the strip of paper bearing the walking footprints and heelprints is still in place.

The double frame is of sufficient height (1 inch [2.5 cm.]) so that only the weight-bearing surface of the rubber is in contact with the paper, the elasticity of the rubber keeping the other inked surfaces from coming in contact with the paper.

Thus one is able to record footprints and heelprints rapidly without ink touching the feet and heels of the patient, and the records are clear



A new device for footprinting and heelprinting. *A* depicts the device, *B*, indicates a child standing on the rubber surface at the line of the hinges, *C* shows the hinged end turned up against the inked surface so that the pressure from a roller may record the heelprints, and *D* shows the double frame turned back and the strip of paper bearing the walking footprints and heelprints in place.

and accurate. When it is desired to photograph the records, it is well to use black ink.

COMMENT

This device has enabled me to make and keep on file the record of every child who has come to my office and who was old enough to walk. The records are indisputable evidence of the condition of the feet at any given time. In another paper I have discussed a method of analyzing footprints and heelprints and of classifying weak feet.

The device can be constructed cheaply; the paper is inexpensive, and the rubber covering can be replaced at a nominal cost.

The value of accurate recording of the footprints has been discussed by King.[1] It might be added that the psychologic effect of the record is not lost on an interested mother.

205 Exchange Building.

CLASSIFICATION OF WEAK FEET IN CHILDREN AND A METHOD OF ANALYZING FOOTPRINTS AND HEELPRINTS

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In order to conduct a problem of research concerning the extent and degree of weakness of the feet in children and to watch the progress over a period of years, both with and without corrective measures, it was necessary to work out a method of classification which would be reasonably simple and accurate. The measurements were to be charted and the children watched over a long period to determine whether the condition improved, remained stationary or became worse. The method developed is useful in watching the progress of children with weak feet on whom corrective measures have been instituted.

The method is based on two considerations: first, the appearance of the foot while bearing weight and while walking, as shown in the walking footprint, and, second, the degree of pronation at the ankle as seen on observation and on examination of the heelprint. A method of accurately measuring the degree of pronation will be explained. I believe that the extent of pronation has much to do with the potential weakness of the longitudinal arch, since the weight of the body is shifted inward when any degree of pronation exists, thus tending to cause the longitudinal arch to sag. This is usually accompanied by abduction of the foot which further embarrasses the effort of the tibialis anticus muscle to balance the foot in the position of slight adduction and supination.

The method of heelprinting has been described [1] previously and will not be discussed here. The various steps in the measurement of the angle of pronation are illustrated in figure 1, and examples of corresponding walking footprints are shown. It has been demonstrated that a line drawn through the center of the calf of the leg passes through the center of the heel (with slight variations) in a normal foot. This line will be referred to as the base-line. The angle formed by the intersection of the base-line and a line drawn through the center of the heel will be designated as the angle of pronation. Figure 1 illustrates the measurement of the angle of pronation.

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1. Bivings, Lee: Heel Printing in Flat Feet, Am. J. Dis. Child. **46**:1050 (Nov.) 1933.

The angle of pronation in a perfect foot should not exceed 5 degrees. Theoretically there should be no angle, but it is unusual to see a foot in which there is not some pronation.

In figure 2 a method of analyzing the walking footprints is illustrated. The longitudinal axis of the heel is found by measuring the full length of the footprint and marking one fourth of that distance

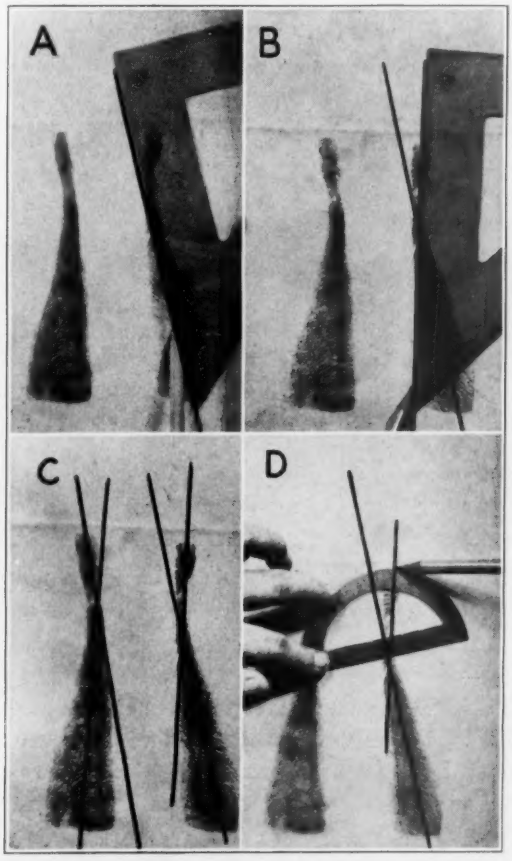

Fig. 1.—Steps in the measurement of the angle of pronation. *A* shows a line drawn through the center of the print representing the calf of the leg, forming the base-line. *B* shows the line drawn through the center of the heel intersecting the base-line at a point at which the print of the achilles' tendon diverges from the base-line. *C* shows the angle formed by the intersecting lines, which is referred to as the angle of pronation. *D* shows the method of determining the angle of pronation by centering a protractor on the base-line and reading off the angle.

from the back of the heel forward. At this point a cross-line is drawn, and its center is measured. Thus is determined the center of the long axis of the heel at approximately the junction of the calcaneocuboid

and the astragaloscaphoid joint. It is along this junction that abduction of the anterior part of the foot on the posterior part takes place. A line is drawn from the center of the heel forward through the point just determined; the area of the footprint through which the line passes forward to and past the toes gives a fairly accurate idea of the extent of abduction of the forefoot on the heel, which is held in a vise so far as lateral movement is concerned by the tibia and fibula. This line will be referred to subsequently as the footprint line.

It is useful in determining the potential weakness in feet which are sagging but which do not sag sufficiently for the under-surface of the longitudinal arch to register on the footprint. This is shown by the angle of pronation in the heelprint.

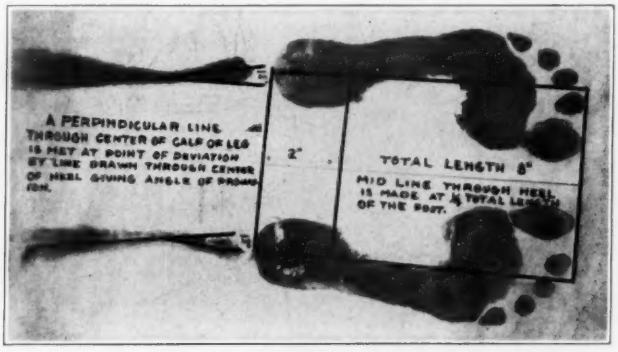
A PERPINDICULAR LINE
THROUGH CENTER OF CALF OR LEG
IS MET AT POINT OF DEVIATION
BY LINE DRAWN THROUGH CENTER
OF HEEL GIVING ANGLE OF PRONA-
TION.
2"
TOTAL LENGTH 8"
MID LINE THROUGH HEEL
IS MADE AT ¼ TOTAL LENGTH
OF THE FOOT.

Fig. 2.—A method of analyzing walking footprints.

In figure 3, *A* shows footprints and heelprints of unusually strong feet, with the footprint line passing out just external to the fifth toe. The heelprints show practically a straight line through the calf of the leg and the heel. *B* shows the footprint line passing out through the fourth toe of the left foot and through the third toe of the right foot. As the foot becomes abducted, as it is in any degree of weakness, the line passes out nearer the inside of the foot. The heelprint of the left foot shows an angle of 9 degrees and that of the weaker, right foot shows an angle of 12 degrees. It is noted that an increase in the angle of pronation shows a corresponding amount of abduction of the foot, as shown in the footprint line in the footprint. *C* shows the footprint line passing out through the third toe with the heelprints showing 10 and 14 degrees of pronation, respectively. *D* shows the footprint line passing out near the first or great toe, showing a marked degree of abduction in a very weak foot. The heelprints show an angle of 14 and 20 degrees, respectively. It is interesting to note that increased abduction always shows some degree of increased pronation in the heel.

After studying the feet of several hundred children I have arrived at the following arbitrary classification:

1. Perfect feet, with no abduction and no pronation (fig. 3 *A*).

2. Feet with first degree weakness, with the footprint line passing out approximately through the fourth toe, and the angle of pronation not exceeding 10 degrees (fig. 3 *B*).

3. Feet with second degree weakness (borderline), with the footprint line passing out through approximately the third toe and the angle of pronation not exceeding 14 degrees (fig. 3 *C*).

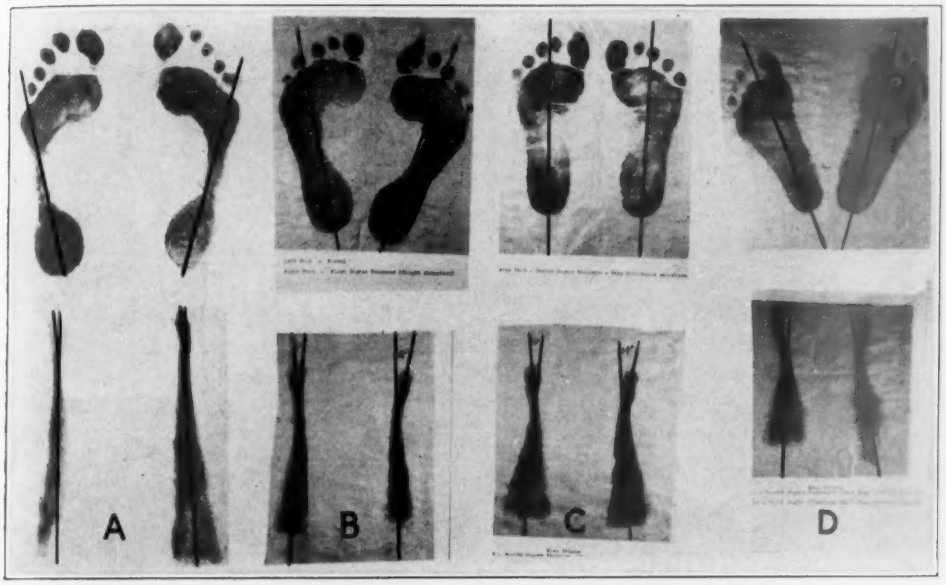

Fig. 3.—*A* shows footprints and heelprints of unusually strong feet; *B* shows prints indicating first degree weakness; *C* shows prints indicating second degree weakness, and *D* shows prints of extremely weak feet.

4. Feet with third degree weakness, with the footprint line passing out near the great toe and the angle of pronation exceeding 14 degrees (fig. 3 *D*).

Since there are relatively few perfect feet I have included those with first degree weakness under the heading of normal feet and refer to them thus in tables 1 and 2.

Table 1 shows the results of the classification by ages in a study of the feet of 923 children between the age of 1 and 4 years.

It will be noted that the percentage of normal feet declined nearly half between the twelfth and eighteenth months and that the percentage of feet with third degree weakness nearly doubled during the same interval.

This suggests that the weakness in the ligaments, tendons and muscles controlling the feet shows most plainly at the age when children begin to walk and the feet bear weight for the first time. There was an increase of 10 per cent in the number of feet with second degree weakness during the same time interval. It is possible, however, that the numbers are insufficient to permit the drawing of definite conclusions, and further study is being made.

Table 2 is a summary of table 1.

If one combines the two groups of weak feet it will be seen that 58 per cent, or more than half the children, had some degree of weakness.

TABLE 1.—*Classification by Age of the Feet of 923 Children*

Age, Year	Normal	With Second Degree Weakness	With Third Degree Weakness	
1	66 (50%)	49 (38%)	16 (13%)	131
1.5	45 (27%)	80 (48%)	43 (25%)	168
2	63 (35%)	72 (48%)	47 (25%)	182
3	67 (37%)	73 (43%)	43 (14%)	183
4	145 (56%)	80 (30%)	34 (14%)	259

TABLE 2.—*Classification of Feet of 923 Children*

Classification	Number	Percentage
Normal	386	42
With second degree weakness	354	38
With third degree weakness	183	20

COMMENT

The placing of the footprint line is not as accurate as the determination of the angle of pronation, on which the classification is actually based. However, by means of the former one is able to arrive at approximately the central longitudinal axis of the heel, and the extension of this line gives a better idea of the relation of the heel and the anterior portion of the foot or the extent of abduction of the anterior portion on the posterior portion of the foot.

The greatest use of the actual measurement of the angle of pronation and the drawing in of the footprint line is to demonstrate improvement after corrective measures have been instituted. It also furnishes a basis for research into the result of wearing a certain type of shoes and the result of wearing no shoes and an accurate method of following the development of the foot from the first walking age to maturity. It eliminates guesswork, for one is able to demonstrate graphically the amount of improvement or the lack of it by comparing records.

205 Exchange Building.

CAPILLARY DEVELOPMENT AND ITS RELATION TO THE INTELLIGENCE OF CHILDREN WITH MONGOLISM

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AND
MAURICE GROZIN, M.D.
NEW YORK

In a previous communication by one of us [1] and in the excellent studies of Müller,[2] Jaensch [3] and others, it has been shown that the cutaneous capillaries reach the mature form of development between the ages of 6 months and 1 year. After this time the morphologic structure of the capillaries remains constant, though the loops may lengthen and become wider in caliber during the advancing years. It has also been shown by Doxiades and Pototzky,[4] Jaensch,[5] Hoepfner,[6] Powdermaker [7] and others that the capillaries in persons with mongolism do not develop normally. They are markedly delayed in growth and rarely reach normal, mature forms. Occasionally one finds normal capillaries (Pototzky,[8] Karger [9]), but this is rare. Instead, one finds

From the Department of Pediatrics, Mount Sinai Hospital, service of Dr. Béla Schick.

1. Leader, Sidney D.: Capillary Microscopy in Children, Am. J. Dis. Child. **44**:403 (Aug.) 1932.

2. Müller, Otfried: Die Kapillaren der menschlichen Körperoberfläche in Gesunden und Kranken, Stuttgart, Ferdinand Enke, 1922.

3. Jaensch, W.: Neue Wege und Möglichkeiten bei Erkennung und Behandlung körperlich-geistig Minderwertiger und Schwacher, Deutsche Ztschr. f. öff. Gsndhtspflg. **4**:171 (Sept.-Dec.) 1928.

4. Doxiades, L., and Pototzky, C.: Die Bedeutung der kardiovasculären Untersuchungsmethoden (Capillaroskopie, Elektrokardiographie, Röntgenographie) für die Beurteilung des Mongolismus und des myxödems beim Kinde, Klin. Wchnschr. **6**:1326 (July 9) 1927. Doxiades, L.: Grundlagen zur Bewertung des kapillaroskopischen Bildes am Nagelfalz bei normalen und geistesschwachen Kindern, Monatschr. f. Psychiat. u. Neurol. **69**:188 (July) 1928.

5. Jaensch, W.: Die Haut Kapillarmikroskopie, Halle, Carl Marhold, 1929.

6. Hoepfner, T.: Die Strukturbilder der menschlichen Nagelfalzkapillaren, Veröffentl. a. d. Geb. d. Med.-Verwalt. **26**:1, 1928.

7. Powdermaker, Florence: Capillary Forms in Relation to Certain Problems in Development, Arch. Neurol. & Psychiat. **22**:1207 (Dec.) 1929.

8. Pototzky, Carl: Die klinischen Ergebnisse der Kapillaroskopie bei neuropathischen und geistesschwachen Kindern, Monatschr. f. Psychiat. u. Neurol. **69**: 188, 1928.

9. Karger, P.: Die klinische Bedeutung des kapillaroskopischen Bildes am Nagelfalz von Kindern, Monatschr. f. Kinderh. **42**:292, 1929.

all sorts of bizarre capillary patterns, and many of the primitive characteristics of the capillaries, such as the subpapillary plexus, undifferentiated venous and arterial limbs and wavy corium, are retained.

In some cases of mongolism the pathologic nature of the capillaries is more marked than in others. Hoepfner,[6] in his classification, divided the abnormal forms into various groups according to the maturity of their development. Thus, if the capillaries retain the characteristics of the subpapillary plexus, even though some evidence of capillary loops is present, they are considered primitive. In this group, the corium is usually flat. The more advanced or intermediate type of capillaries, according to Hoepfner, have a large caliber and are broad, turret-shaped and saddle-shaped, with undifferentiated venous and arterial limbs. The corium is wavy. In the most advanced or mature stage of pathologic development, the capillaries deviate from the normal in size, shape and arrangement. The corium is scalloped, there is a differentiation between the venous and arterial branches and there is no evidence of the primitive or subpapillary plexus.

At times we have found it difficult to classify our capillary patterns definitely in this fashion, since the forms frequently present elements of the various stages between the primitive and the mature. Pototzky attempted to subdivide his cases of mongolism into groups according to whether or not an endocrine element was present. He contended that certain children are amenable to glandular therapy. However, although these children improve mentally and physically, the structure of the capillaries does not change materially.

We have studied twenty-two children with established mongolism from various aspects, and this paper describes our studies of the capillaries and attempts to correlate the observations with the intelligence of the patients as evidenced by intelligence tests performed according to the Terman [10] modification of the Binet-Simon system and the Gesell [11] method.

A number of the children were observed for two years, and studies of the capillaries as well as of the psychophysical make-up were made at varied intervals. The results are shown in table 1.

REPORT OF CASES

A brief review of some of the cases may be of interest.

CASE 1.—A. A., was observed by us for two years. His intelligence quotient remained at 20, and the capillary pattern did not change. The capillaries were fairly well preserved, though obviously of pathologic development.

10. Terman, Lewis M.: The Measurement of Intelligence, Cambridge, Mass., Riverside Press, 1916.

11. Gesell, Arnold: The Mental Growth of the Pre-School Child, New York, The Macmillan Company, 1930.

TABLE 1.—*Studies of the Capillaries of Twenty-Two Children with Mongolism*

No.	Name	Age	Sex	Intelligence Quotient	Capillaries	Follow-Up: Intelligence Quotient	Follow-Up: Capillaries
1	A. A.	8½ yr.	M	5/6/31: 20	5/12/31: tortuous, long, irregular; no subpapillary plexus; many bizarre forms; mature type	10/8/31: 20 5/28/32: 20	5/28/32: no change in pattern
2	E. W.	10½ yr.	F	9/8/31: 40	9/8/31: tend to approximate normal; regular hairpin loops; no anastomosis; slight tortuosities of the vessels; normal corium; mature type	12/17/31: 51	11/10/32: no change; practically normal except for occasional bizarre mature forms approaching maturity
3	C. P.	11 yr.	F	6/13/31: 30	6/13/31: to a great extent normal, however, many distorted forms; no subpapillary plexus; corium normal; mature type		
4	S. M.	6 mo.	M	5/28/31: 25	5/28/31: no true loops; subpapillary plexus present; corium not developed; "primitive type"	Died on 10/23/31	
5	E. M.	13½ yr.	M	6/11/31: 28	6/11/31: irregular, tortuous, large corkscrew loops; some turret-shaped and saddle-shaped subpapillary plexus; corium underdeveloped; vessels thin, increased in number; intermediate type		
6	Z. M.	10 yr.	F	5/2/31: 45	5/2/31: normal in structure and development; only occasional evidence of abnormal or immature forms; mature, hypoplastic type		
7	J. G.	15 yr.	M	5/15/31: 30	5/16/31: irregular, immature forms; no subpapillary plexus; primitive type		
8	J. K.	6½ yr.	M	5/21/31: 20	5/23/31: irregular, of wide caliber but tending toward normal growth; intermediate type		
9	G. G.	18½ mo.	M	6/2/31: 35	6/2/31: bizarre, tortuous, long and thin; subpapillary plexus present; corium wavy; primitive type	6/9/32: 45	6/9/32: no change in structure
10	S. E.	10 yr. and 2 mo.	M	6/2/31: 47	7/7/31: corium normal; vessels long and narrow; occasionally bizarre; no subpapillary anastomosis; mature type	2/16/32: 50 4/20/33: 59	4/20/33: practically normal; loops normal except for occasional distorted forms
11	J. E.	10 yr. and 2 mo.	M	7/7/31: 57	7/7/31: corium normal; no evidence of subpapillary plexus; vessels slightly tortuous, otherwise normal in size and number; no evidence of arrested development; mature type	4/20/33: 56	4/20/33: almost normal except for occasional bizarre forms

TABLE 1.—*Studies of the Capillaries of Twenty-Two Children with Mongolism—Continued*

No.	Name	Age	Sex	Intelligence Quotient	Capillaries	Follow-Up: Intelligence Quotient	Follow-Up: Capillaries
12	M. G.	2 yr.	F	9/13/31: 20	9/13/31: unusually long, slightly tortuous; a few modified primitive and bizarre forms are present; corium normal; mature type	11/3/32: 30 11/22/32: 37 2/3/33: 40	11/3/32: same as on previous examination; occasional grotesque forms
13	M. B.	5 mo.	M	12/29/31: 35	12/29/31: loops irregularly formed, turret-shaped; many branching and tortuous forms; subpapillary plexus prominent; corium flat; primitive type	11/17/32: 50	11/17/32: similar to previous examinations; primitive type
14	A. C.	8 yr.	F	12/3/31: 30	12/3/31: irregular, showing bizarre corkscrew shapes irregularly placed; evidence of subpapillary plexus; corium wavy; intermediate type	1/26/33: 41 10/14/33: 55	10/14/33: slight evidence of improvement
15	S. K.	3 yr. and 2 mo.	M	1/21/32: 40	1/21/32: rather long, tortuous, irregularly shaped; no bizarre forms; subpapillary plexus present; corium practically normal; intermediate type	10/27/32: 50	10/29/32: similar to previous examination
16	V. N.	4 mo.	F	2/18/32: 20	2/18/32: subpapillary plexus present; sprouting capillary forms irregular, tortuous, showing beginning of bizarre shapes; corium flat; primitive type		
17	C. M.	5 yr. and 2 mo.	M	4/19/32: 20	4/19/32: long tortuous, irregular; many bizarre forms; subpapillary plexus present; corium wavy; intermediate type		
18	N. K.	6½ yr.	F	6/2/32: 10	6/2/32: a marked subpapillary plexus; a few true capillary loops, irregular, tortuous and bizarre; corium flat; primitive type		
19	M. S.	1 yr. and 8 mo.	M	6/9/32: 20	6/12/32: long, tortuous, distinct; occasional bizarre forms; subpapillary plexus present; corium somewhat scalloped; intermediate type	11/3/32: 46 3/23/33: 46 2/23/33: 46	11/3/32: similar to previous examination; no change
20	R. C.	1 yr. and 8 mo.	M	11/10/32: 25	11/10/32: only anlage of capillaries present; subpapillary plexus present; corium flat; primitive type	10/4/32: 26	10/4/32: no further progress in development of vessels
21	S. B.	5 yr.	M	1/12/33: 45	1/12/33: rather long, tending to assume normal hairpin-shaped loops; occasional bizarre forms; some evidence of subpapillary plexus; corium scallop-shaped; mature type		
22	M. M.	3½ mo.	M	4/27/33: 42	4/27/33: corium wavy; subpapillary plexus present; no differentiation between arterial and venous limbs; occasional bizarre, mature forms; intermediate type		

CASE 4.—S. M. is of great interest because, to our knowledge, no studies of the capillaries have heretofore been made on a Negro with mongolism. The child died a short time after observation, of a congenital cardiac condition.

CASE 6.—Z. M. had a relatively high intelligence quotient. Her capillaries were more nearly normal than those of any other member of the group.

CASES 10 and 11.—S. E. and J. E. were male twins. Observations on these children have been reported by Reuben and Klein.[12] Mongolism in both twins is rare. Only twelve instances have been reported in the literature (Rosanoff and Handy [13]) in which both twins were affected. The case of S. E. and J. E. is probably the first in which studies of the capillaries have been made. The intelligence of these children was above the average for children with mongolism, and their capillaries were mature, though of pathologic development. They were monozygotic twins; their physical characteristics were similar, and their capillary patterns were identical.

CASE 14.—A. C. in a two year follow-up showed marked improvement in mental development. The capillaries, which were of the intermediate pathologic type, showed little improvement.

CASE 18.—N. K. had the lowest intelligence quotient of the group. The capillaries, too, were in the earliest stage of development.

CASE 19.—M. S. showed great improvement in intelligence after two years. The capillary pattern had not changed.

COMMENT

Before entering into a discussion of our results it would be advisable to review briefly the development of the capillaries in the normal person.

At birth there are no capillary loops. The structure of the vessels consists of a primitive network called the subpapillary plexus, which is supplied by the arterioles and venules of the deeper layer of the skin. The corium is flat. As the child grows older the saddle-shaped forms sprout from the plexus and gradually develop into slender, hairpin-like capillary forms, with a differentiation between the arterial and the venous limbs. At the same time the subpapillary plexus gradually disappears, and the corium assumes a scalloped appearance. The development of the capillaries in persons with mongolism tends to go through these stages, but in a bizarre and delayed fashion. In some cases the subpapillary plexus is retained through adult development. In other cases the capillary forms are distorted, in others the differentiation between the arterial and venous limbs does not exist, and in still others the corium remains flat or wavy and does not assume the scalloped appearance.

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12. Reuben, Mark S., and Klein, Sidney: Mongolian Idiocy in Both Twins, Arch. Pediat. **43**:552, 1926.

13. Rosanoff, A. J., and Handy, L. M.: Etiology of Mongolism with Special Reference to Its Occurrence in Twins, Am. J. Dis. Child. **48**:764 (Oct.) 1934.

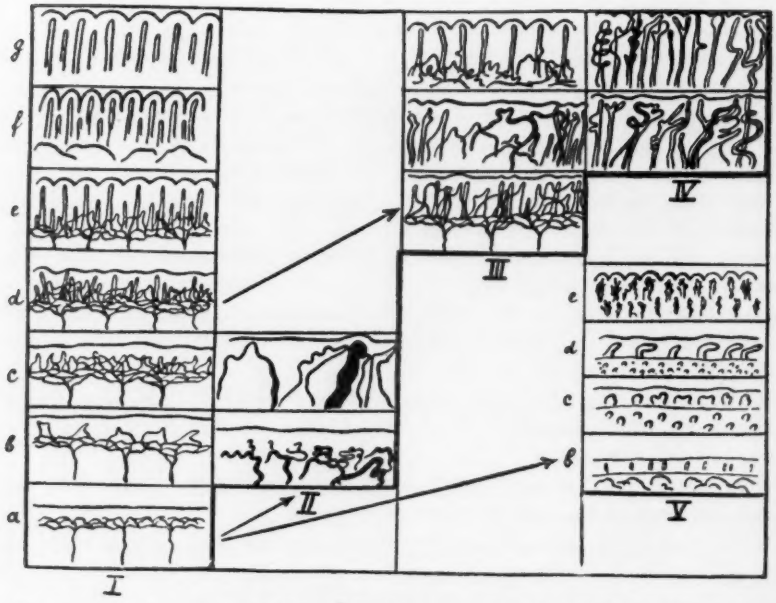

Fig. 1.—Development of skin capillaries, normal and pathologic (Jaensch and Hoepfner). Column *I* shows the following normal development: *a*, primitive network with flat-shaped corium observed shortly after birth; *b* and *c*, saddle-shaped and turret-shaped loops sprouting at from 5 to 6 weeks of age; *d*, *e* and *f*, formation of hairpin loops, differentiation of venous and arterial components, development of scalloped corium and disappearance of subpapillary plexus; *g*, mature form reached at from 6 months to 6 years of age. Columns *II*, *III*, *IV* and *V* show abnormal forms derived from the various stages of development.

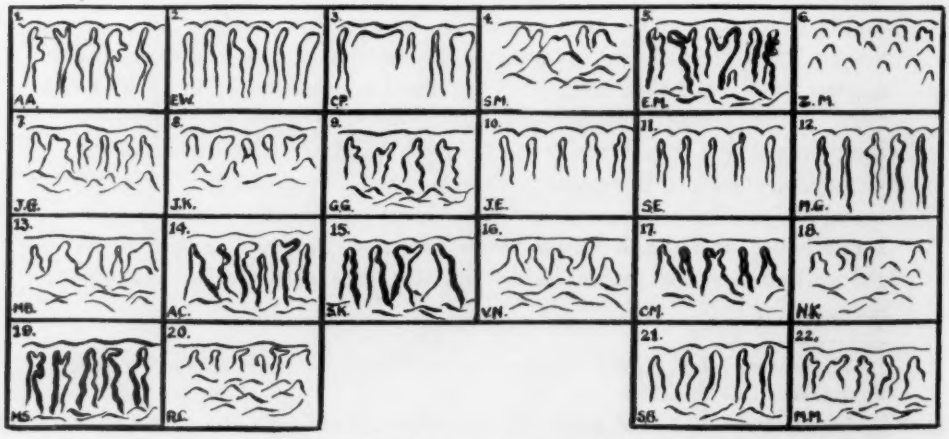

Fig. 2.—Skin capillaries of twenty-two children with mongolism.

The method used in this study of the capillaries of the skin was that described by one of us.[1] For purposes of uniformity the nail bed of the middle finger of the right hand was used for examination.

In this series of twenty-two cases, all the children had capillaries that were abnormal in some phase of their development. In some, this trend was more marked than in others. In one case, the capillaries were normal save for an occasional distorted loop.

The children were mentally defective to a marked degree, the highest intelligence quotient being 57. Obviously, it is almost impossible

TABLE 2.—*Analysis of the Capillaries and Their Relation to Intelligence*

Stage of Capillary Development	Intelligence Quotient Less Than 25		Intelligence Quotient More Than 25	
	Number of Cases		Number of Cases	
Primitive	4	45	3	23
Intermediate	3	33	4	30
Mature	2	22	6	47
Total	9		13	

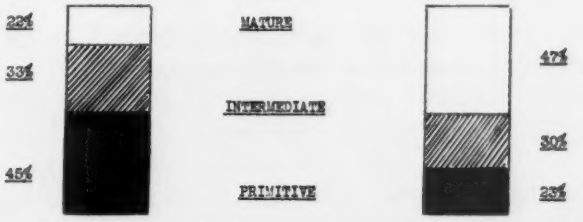

Fig. 3.—Analysis of the capillaries and their relation to the intelligence of the children. The column on the left shows the rating of those with an intelligence quotient less than 25 and that on the right the rating of those with an intelligence quotient more than 25.

to divide persons with mongolism into the more and the less intelligent, but arbitrarily we have classified the group in two divisions—those whose intelligence quotients were under 25 and those whose intelligence quotients were over 25. Of the former group four, or 45 per cent, had capillaries of the primitive type, whereas of the latter group only three, or 23 per cent, had primitive capillaries. Of the less intelligent group, two, or 22 per cent, had mature capillaries, as compared with six, or 47 per cent, of the children with a higher intelligence quotient.

It is nevertheless obvious that all the children had some evidence of pathologic development of the capillaries, regardless of the degree of mental deficiency. Thus, in the children whose intelligence appeared to be higher than that of the average person with mongolism the capillaries, in the main, more nearly approached normal. In those with extreme mental deficiency, the capillaries appeared to be in the more

primitive stages of development. Powdermaker [7] made observations similar to these in her group of thirty-four persons with mongolism. However, in a few of our cases this did not hold true. In the children whom we have followed over a period of two years the capillary elements have not matured to any great degree, in spite of the fact that in some of the children there has been a marked improvement in the intelligence.

From these studies, then, one cannot come to a definite conclusion regarding the correlation between the mental development and the development of the capillaries of children with mongolism.

It is apparent that one cannot use the degree of development of the capillaries as an index of mental development in mongolism, in spite of the fact that there seems to be a correlation between them.

SUMMARY

Studies of the capillaries and psychologic tests were made on twenty-two children with mongolism.

All the children had some evidence of abnormal development of the capillaries.

Although there seems to be a correlation between the mental development and the development of the capillaries, this is not definite in all cases.

BLOOD IN THE STOOLS OF THE NEW-BORN

AN UNEXPLAINED SYMPTOM

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From July 1932 to April 1934 I have observed 20 new-born infants showing blood in the stools as the only abnormality. These babies were born at the Multnomah County Hospital. During this period from 50 to 86 babies were born each month, making a total of 1,503.

Blood was observed in the stools usually about the sixth day of life, occasionally on the third day and once on the ninth day. Blood was seen for one day, and never for more than two days. In 6 cases whole blood was given intramuscularly or subcutaneously and the bleeding promptly stopped; likewise in 14 cases in which blood was not given, the bleeding stopped almost at once.

The appearance was that of fresh blood, usually mixed with mucus and fecal material, apparently coming from the lower portion of the intestinal tract. The quantity of blood varied from streaks to as much as 20 to 30 cc. The stools of other infants in the nursery at the time were examined for occult blood, with negative results. The benzidine test was used to detect the presence of blood.

All the infants in whose stools blood was noted were normal and healthy in every other respect. None of them were premature. Their weight at birth ranged from 2,450 to 4,345 Gm. Ten of the 20 were boys and 10 were girls. All the babies were entirely breast fed. No evidence of fissures or abrasions was noted in the mothers' nipples. The nipples were washed with physiologic solution of sodium chloride before each nursing. None of the mothers received purgatives at the time of these observations. Blood from the mothers and their babies gave negative reactions to Kolmer and Kahn tests. None showed more than the average physiologic jaundice. The bleeding and the clotting time when tested were within normal limits. The bleeding time was estimated on blood obtained by puncture of the heel, and the clotting time by capillary tube and with a drop of blood on a glass slide, a pinpoint being used to determine the time at which clotting took place. Rectal and proctoscopic examinations gave negative results. The stools of 5 of the infants were cultured but failed to give evidence of any organism of the dysentery group. All the babies remained well, showing no further sign of bleeding.

The condition was observed during all seasons of the year and was absent for periods of months. During this two year period 5 typical

cases of hemorrhagic disease of the new-born were observed. Other lying-in hospitals of the city were investigated without finding a similar condition. The appearance of blood in the stools of a new-born infant is spectacular enough to cause any present-day nurse to note the condition.

In attempting to explain the symptom of blood in the stools of an otherwise healthy infant, it was at first suspected that some injury to the rectum had been caused by the use of the thermometer. This possibility was carefully checked and ruled out.

Dysentery was ruled out by the fact that the infants were not sick and had normal temperatures, that only 1 or 2 infants were affected

Observations on the Blood of Twenty Infants with Blood in the Stools

Case	Date of Birth	Sex	Weight at Birth, Gm.	Day of Life on Which Blood Appeared in Stools	Treatment, Injection of Whole Blood (Father's), Cc.	Kolmer and Kahn Reactions	Bleeding Time	Clotting Time	Culture of Stools for Organisms of Dysentery Group
1	7/24/32	M	2,760	7 and 8	100	Neg.	.....	.....	.....
2	9/ 5/32	F	3,590	6	50	Neg.	.....	.....	.....
3	11/ 1/32	M	3,100	6	30	Neg.	.....	.....	.....
4	11/ 6/32	F	3,190	6	None	Neg.	.....	.....	.....
5	11/21/32	M	2,540	8 and 9	20	Neg.	.....	.....	.....
6	11/25/32	M	3,100	5	None	Neg.	.....	.....	.....
7	12/ 7/32	M	3,670	6	None	Neg.	.....	.....	.....
8	1/21/33	F	3,200	6	None	Neg.	.....	.....	Neg.
9	2/10/33	F	3,450	4 and 5	None	Neg.	5 min., 45 sec.	7 min., 30 sec.	Neg.
10	2/27/33	M	3,050	8	None	Neg.	.....	.....	Neg.
11	3/ 3/33	M	3,410	5	None	Neg.	.....	.....	.....
12	3/15/33	F	3,000	6	None	Neg.	1 min., 30 sec.	6 min., 30 sec.	Neg.
13	3/18/33	M	3,000	5	None	Neg.	.....	.....	Neg.
14	5/20/33	F	2,450	3	30, 10 and 20	Neg.	6 min., 30 sec.	4 min., 45 sec.	.....
15	5/23/33	F	3,180	2	25 and 20	Neg.	7 min., 30 sec.	6 min.	.....
16	10/14/33	M	4,345	3	None	Neg.	2 min., 10 sec.	4 min., 45 sec.	.....
17	12/14/33	F	4,050	5	None	Neg.	2 min., 30 sec.	4 min., 20 sec.	.....
18	3/17/34	M	3,425	5	None	Neg.	2 min., 30 sec.	4 min.	.....
19	4/ 3/34	F	.....	4	None	Neg.	1 min.	6 min., 30 sec.	.....
20	4/ 7/34	F	2,725	4	None	Neg.	.....	.....	.....

in a group of from 18 to 30 in the nursery at the same time and that cultures of the stools of 5 of the infants failed to yield evidence of organisms of the dysentery group.

The first patients with this symptom were promptly given whole blood (father's blood) with the thought that the infants were showing the onset of hemorrhagic disease of the new-born. The appearance of blood in the stools stopped at once. In these first cases the blood did not appear in the stools until the sixth, seventh or eighth day of life, which is rather late for the first appearance of hemorrhagic disease. With some apprehension the next patients were given no treatment (no whole blood), but the bleeding promptly stopped. The bleeding and the clotting time were checked in 8 of the infants and was found to be within normal limits. In 2 of the later cases, in which the bleeding began on the third and the second day of life, respectively, whole blood was injected, and there was no further appearance of the symptom.

The bleeding time was six minutes and thirty seconds in one and seven minutes and thirty seconds in the other. In another case, in which there was a bloody stool on the third day of life, no blood was injected, and the bleeding stopped at once.

Twenty cases in a series of 1,503 infants observed consecutively is rather high for the average incidence of hemorrhagic disease of the new-born, especially since during this same time 5 typical cases of hemorrhagic disease were observed which are not included in this series.

The accompanying table gives the observations on the cases.

In a personal communication Dr. Clifford Grulee related an experience similar to that just outlined which he had five or six years ago. He said: "At that time, we could not find any cause for the blood in the stools try as hard as we could. The condition stopped suddenly, and we have not been in contact with it since. I do not know how to explain it, but I think it is something more than a coincidence."

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CONTOUR OF THE CHEST IN CHILDREN

IV. ACCORDING TO NATIONALITY

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MINNEAPOLIS

The relation between constitutional characteristics and race has been discussed in the literature by many investigators without any definite conclusions being reached. The studies by Sofer,[1] Paulson,[2] Stern-Piper,[3] Pfuhl,[4] Weidenreich[5] and von Verschuer[6] lead one to believe that there are no definite physical racial characteristics which appear in every individual, although certain characteristics may predominate in various racial groups.

The purpose of this report was to investigate the contour of the chest in groups of children of various nationalities and to compare the thoracic indexes to determine whether in the field of development of the chest there are not some noticeable differences. The ancestry of about eight thousand Minneapolis school children was obtained. The children were classified into eleven groups, and the average thoracic index and the total number of subjects for each group is given in tables 1 and 2. The groups were: Scandinavian, German, Russian and Polish, Jewish, English, Irish, French, Balkan, Scotch, Italian and Negro.

On examining the average thoracic index for each age group for every nationality as given in tables 1 and 2, one will observe that there is no appreciable difference in the thoracic index curves for the various groups. However, a close study of the tables reveals perhaps some slight differences.

AVERAGE THORACIC INDEX CURVES FOR GIRLS

The girls of Scandinavian descent presented a satisfactory thoracic index curve (graph, *e*). The curve is almost a duplicate of the curve

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From the Department of Medicine, University of Minnesota.

1. Sofer, L.: Beiträge zur Rassenphysiologie und Rassenpathologie, Polit.-Anthrop. Rev. **8**:337, 1909.
2. Paulson, J.: Weisen und Entstehung der Rassenmerkmale, Arch. f. Anthrop. **18**:60, 1921.
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4. Pfuhl, W.: Die Beziehungen zwischen Rassen- und Konstitutionsforschung, Ztschr. f. d. ges. Anat. (Abt. 2) **9**:172, 1923.
5. Weidenreich, F. : Rasse und Körperbau, Berlin, Julius Springer, 1927.
6. von Verschuer, O.: Zur Frage Körperbau und Rasse, Ztschr. f. d. ges. Anat. (Abt. 2) **11**:754, 1925.

TABLE 1.—*Average Thoracic Indexes for Girls of Various Nationality Groups*

Nationality	Age, Years									
	5	6	7	8	9	10	11	12	13	14
Scandinavian										
Thoracic index	719	721	706	694	703	692	700	692	683	681
Number of cases	31	100	197	187	225	203	199	120	43	18
German										
Thoracic index	751	727	706	694	706	686	697	700	690	731
Number of cases	12	47	48	74	87	72	86	44	21	5
Russian and Polish										
Thoracic index	709	706	706	714	706	687	700	700	682	681
Number of cases	22	39	59	75	85	40	48	47	32	27
Jewish										
Thoracic index	704	715	719	706	709	701	691	703	734	694
Number of cases	4	36	43	56	66	36	52	34	4	4
Irish										
Thoracic index	720	721	700	718	692	706	707	721	681	731
Number of cases	4	10	21	20	27	43	27	18	7	3
English										
Thoracic index	703	725	691	707	700	694	692	687	700	573
Number of cases	2	14	16	30	29	24	30	20	5	1
French										
Thoracic index	705	750	721	714	676	683	684	697	669	695
Number of cases	2	7	8	19	15	21	16	8	4	3
Balkan										
Thoracic index	728	713	686	719	722	683	692	692	697	711
Number of cases	6	14	20	17	18	14	21	19	8	4
Scotch										
Thoracic index	...	704	706	722	722	694	703	714	...	...
Number of cases	..	4	3	11	8	14	4	3	..	..
Italian										
Thoracic index	700	700	717	722	689	667	720	737	...	...
Number of cases	1	5	6	8	4	4	2	1	..	..
Negro										
Thoracic index	...	697	723	736	714	707	710	706	800	712
Number of cases	..	3	6	6	10	6	6	3	2	9

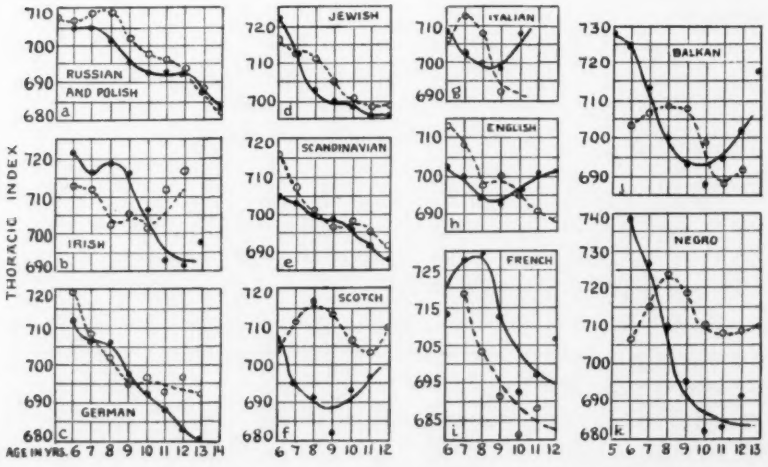
TABLE 2.—*Average Thoracic Indexes for Boys of Various Nationality Groups*

Nationality	Age, Years									
	5	6	7	8	9	10	11	12	13	14
Scandinavian										
Thoracic index	733	706	703	703	694	694	694	699	683	728
Number of cases	29	190	154	217	245	249	222	148	77	24
German										
Thoracic index	724	714	711	697	711	684	683	690	675	694
Number of cases	9	61	53	66	87	71	73	60	31	8
Russian and Polish										
Thoracic index	736	705	706	704	694	686	700	692	690	683
Number of cases	15	46	68	66	83	72	51	41	38	27
Jewish										
Thoracic index	686	733	703	704	703	694	700	692	707	695
Number of cases	2	42	42	58	60	58	62	39	10	8
Irish										
Thoracic index	686	727	711	711	736	700	683	694	700	675
Number of cases	5	21	19	27	43	35	31	23	15	9
English										
Thoracic index	726	702	705	694	686	703	700	701	704	711
Number of cases	2	13	20	21	25	43	25	20	3	4
French										
Thoracic index	795	702	739	744	703	692	681	718	678	694
Number of cases	4	10	10	4	13	30	17	14	8	4
Balkan										
Thoracic index	733	722	719	700	680	703	684	697	729	667
Number of cases	11	12	11	20	18	23	16	10	11	7
Scotch										
Thoracic index	657	714	694	676	703	667	710	696	...	756
Number of cases	1	11	5	7	9	9	8	4	..	1
Italian										
Thoracic index	...	702	722	686	692	720	716	658	634	684
Number of cases	..	10	5	7	5	6	4	2	3	1
Negro										
Thoracic index	722	749	718	714	632	697	675	675	699	750
Number of cases	2	6	9	9	1	6	7	4	4	1

for the nineteen thousand school children of Minneapolis, shown in my first report.[7] The average thoracic index was about 72 at the age of 5, and the chest gradually flattened until a thoracic index of about 68 was reached at maturity. This I consider an almost perfect curve for chest development.

The curve of development for the children of German descent took a course similar to that of the Scandinavian children until the age of 10, at which time the German girls showed a little flatter chest, which continued through the age of 11. From this age the curve for chest development was not quite as good as that of the Scandinavians (graph *a*).

The Russian and Polish girls showed a curve for chest development which was perhaps even better than the curves for the Scandinavians



Average thoracic index curves, according to age, of various nationality groups: *a*, Russian and Polish, 507 boys, 474 girls; *b*, Irish, 228 boys, 180 girls; *c*, German, 519 boys, 496 girls; *d*, Jewish, 381 boys, 335 girls; *e*, Scandinavian, 1,555 boys, 1,323 girls; *f*, Scotch, 55 boys, 47 girls; *g*, Italian, 43 boys, 31 girls; *h*, English, 76 boys, 171 girls; *i*, French, 114 boys, 103 girls; *j*, Balkans, 139 boys, 141 girls; *k*, Negro, 49 boys, 51 girls. The solid lines and circles represent the curves for the boys, and the broken lines and open circles, the curves for the girls. The curves were obtained by one application of the three point rule.

and Germans (graph *a*). The thoracic index was about 71 at the age of 5 and then flattened, being 68 at maturity. This is evidence of perfect development. The number of subjects in this group, however, was about one-third that in the Scandinavian group and almost the same as in the German group.

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7. Weisman, S. A.: Contour of the Chest in Children: I. According to Age, Am. J. Dis. Child. **48**:502 (Sept.) 1934.

The Jewish girls showed good curve chest development (graph, *d*). It will be observed that the course was similar to that of the curves for the aforementioned groups, although the tendency was perhaps toward a slightly deeper chest. The same can be said about Irish girls, except that after the age of 10 there was a tendency to a deeper chest (graph, *b*).

The curves for the children of Scotch, Italian, English, French and Balkan descent show a good contour of the chest (graph, *f*, *g*, *h*, *i* and *j*). The curves are similar to the ideal curves for chest development.

Negro girls, too, showed a fairly normal curve for chest development (graph, *k*). It compares favorably with the average indexes of the other nationality groups.

The curves for the contour of the chest of the Russian and Polish, German, Jewish and Scandinavian boys resembled each other closely (table 2; graph, *a*, *c*, *d* and *e*). These groups had the largest number of subjects. In the other groups the general picture was about the same, especially up to about the age of 10. From this age the tendency seemed to be toward a deeper chest. In the latter groups the number of subjects was small in comparison with the number in the four groups mentioned previously. This factor perhaps accounts for the variations.

One factor, however, is evident. The boys' chests were, as a whole, flatter than the girls', especially in the first four groups mentioned. The correlation of the boys' and the girls' thoracic index curves was similar to that for the nineteen thousand boys and girls from the Minneapolis public schools, reported in an earlier paper.[7]

In the remaining groups the tendency seemed to be about the same. In the French group, however, the girls had flatter chests (graph, *i*). I am of the opinion that if a larger number of subjects was had for these groups the picture would be similar to that shown by the first four groups mentioned.

COMMENT

About eight thousand Minneapolis school children whose ancestry was determined were divided into eleven nationality groups: Scandinavian, German, Russian and Polish, Jewish, English, Irish, French, Balkan, Scotch, Italian and Negro. The average thoracic index according to age was determined for each group, and the values were compared with each other.

On comparing the index curves for the groups having the largest number of subjects it was found that the curves for both boys and girls resembled each other closely. These groups were: Scandinavian, German, Russian and Polish, and Jewish. The remaining groups, having

a smaller number of subjects, showed some variations, but as a whole the thoracic index curves were similar to those of the aforementioned groups.

These studies indicate that there are perhaps no definite differences in the contour of the chest among the various nationality groups as represented among Minneapolis school children.

CONCLUSIONS

The thoracic index curves for the contour of the chest of various nationality groups are presented.

In the various nationality groups among the Minneapolis school children there is a general similarity in the contour of the chest.

Ancestry alone is perhaps not the most important individual factor in good chest development.

VALUE OF INCREASED SUPPLY OF VITAMIN B_1 AND IRON IN THE DIET OF CHILDREN

PAPER II

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AND
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In 1932, one of us (Summerfeldt [1]) reported that when a group of normal children were fed for ten weeks a special cereal mixture rich in vitamin B and various mineral elements in place of the commonly used cereals a marked increase in weight resulted. It was suggested that this increased gain in weight was due to the high vitamin B content of the cereal. In order to obtain further information as to the factor present in this cereal which brought about the increased gain in weight, and also to determine whether the increased gain in weight would be continued for a period longer than ten weeks, the present investigation was undertaken.

INVESTIGATION

Children in a large orphanage were divided into three groups of from twenty to twenty-three children each, the groups containing about equal numbers of girls and boys of similar ages. The ages of the children on the nearest birthday varied from 5 to 14 years. They had been in the institution for at least two months before the period of observation began, so that they had become accustomed to the institutional regimen. All the children were of British descent. The weight and height at the beginning of the period of observation did not deviate by more than 10 per cent from the normal values for the ages given in the tables of the Toronto Health Department.

The diet of the institution was good. The average daily consumption of milk per child was 24 ounces (709.77 cc.). Each child consumed from one to four eggs weekly, depending on the season. Meat was served from three to six times weekly. One or two vegetables were usually served daily in addition to potatoes. Fresh fruit, usually in the form of an apple or occasionally of an orange or pear, was served daily for approximately nine months. During the spring and early summer months dried or preserved fruits were frequently given.

The first, or control, group was kept on the regular diet of the institution. These children received 3 ounces (85 Gm.), by dry weight, of oatmeal or cracked wheat for breakfast each morning. The second group was fed the same diet as the control group with the addition of 6 Gm. of vitamin B concentrate made from

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Read at the Twelfth Annual Meeting of the Canadian Society for the Study of Diseases of Children, June 1, 1934.

From the Department of Paediatrics, University of Toronto, and the Hospital for Sick Children, under the direction of Alan Brown, M.D.

1. Summerfeldt, P.: The Value of an Increased Supply of Vitamin B_1 and Iron in the Diet of Children, Am. J. Dis. Child. **43**:284 (Feb.) 1932.

wheat germ and brewer's yeast. This concentrate supplied 198 Chick and Roscoe [2] units of vitamin B_1 and 96 Chick and Roscoe units of vitamin B_2. The third group received the same diet as the control group except that 3 ounces (85 Gm.) of a precooked form of the special cereal mixture replaced the ordinary cereals for breakfast. Three ounces of this cereal contained 126 Chick and Roscoe units of vitamin B_1 and 81 Chick and Roscoe units of vitamin B_2.

RESULTS

The children were weighed twice a month for a period of six months. In the table is given the average gain in weight of the children in each of the three groups. The average gain in weight of those in the control group fed ordinary cereals was 3.6 pounds (1.63 Kg.), which is slightly greater than the gain that would be expected for these children (3.3 pounds, or 1.5 Kg.). The average gain in weight of the group fed the vitamin B concentrate in addition to the regular diet was 5.5 pounds, or 2.89 Kg. This was a considerable increase over the expected gain of 3.3 pounds. The group in whose diet the special cereal was substituted for

Gain in Weight During a Six Months' Period of Children Receiving the Special Cereal Mixture and of Those Receiving Vitamin B

	Number of Children	Average Deviation from Normal Weight for Age and Height, Lbs.	Expected Gain During Six Months, Lbs.	Actual Gain, Lbs.	Standard Deviation of the Mean
Control group	20	—0.1	3.3	3.6	±0.3
Group receiving vitamin B	22	—0.4	3.0	5.5	±0.5
Group receiving special cereal	23	—0.1	3.1	7.8	±0.4

ordinary cereals showed the greatest gain in weight (7.8 pounds, or 3.54 Kg.), which is 2.3 times the expected gain for this group. The results are graphically shown in chart 1.

The results at the end of the six month period were analyzed statistically according to the method described by Banister,[3] and the standard deviations and the total percentages are given. It is obvious from these values that the results are statistically satisfactory.

Determinations of hemoglobin were made to ascertain what effect the high iron content of the special cereal mixture had on the hemoglobin of these normal children and also to determine whether the vitamin B concentrate had any effect on the production of hemoglobin.

The Newcomer method was used, blood being taken from the finger and the determinations made on the three groups of children at monthly intervals. At the beginning of the investigation, the average hemoglobin content for the control group was 10.4 Gm. per hundred cubic centimeters of blood; for the group receiving vitamin B, 10.1 Gm., and for the group receiving the special cereal mixture, 10.2 Gm. During this six month period, as shown in chart 2, the average hemoglobin content in the control group remained about stationary. The group given vitamin B showed a gain of 0.9 Gm., which is 0.6 Gm. more than that in the control group, while the group given the special cereal mixture showed a gain of 1.8 Gm., or 1.5 Gm. more than that in the control group.

2. Chick, H., and Roscoe, M. H.: Biochem J. **23**:498, 1929.

3. Banister, H.: Elementary Applications of Statistical Method, Glasgow, Blackie & Son, Ltd., 1929.

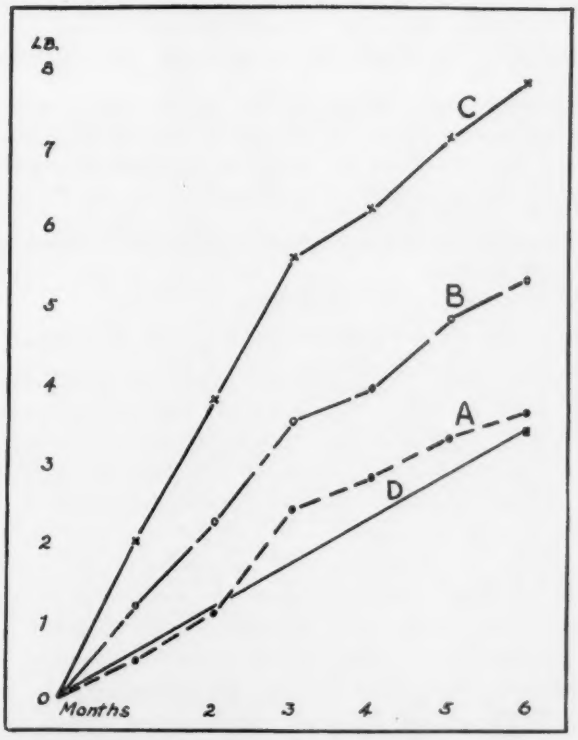

Chart 1.—Effect of special cereal mixture and vitamin B concentrate on the rate of growth of normal children. *A* represents the gain in weight in the control group; *B*, that in the group receiving vitamin B, and *C*, that in the group receiving the special cereal. *D* represents the expected gain in weight.

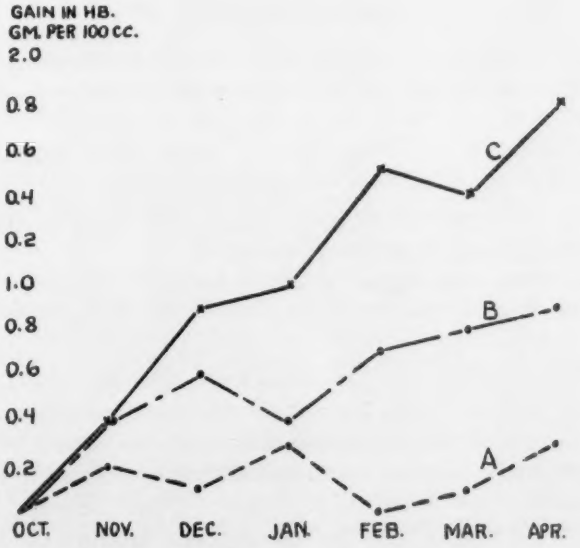

Chart 2.—Average increase in hemoglobin in children fed a special cereal mixture and vitamin B. *A* represents the increase in hemoglobin in the control group; *B*, that in the group receiving vitamn B, and *C*, that in the group receiving the special cereal mixture.

In this investigation the daily intake of iron was the same in the control group and in the group receiving vitamin B, since the concentrate was found by analysis to be free from iron and copper. The amount of iron found in 3 ounces (85 Gm.) of oatmeal was 4 mg.; in 3 ounces of cracked wheat, 5.2 mg., and in 3 ounces of the special cereal mixture, 22 mg. It is thus evident that the substitution of the special cereal mixture for oatmeal or cracked wheat gave a considerable increase in the daily intake of iron.

COMMENT

It is seen from chart 1 that when the group of children who were already receiving a good diet were fed the special cereal mixture they immediately began to gain weight at a more rapid rate than the children of the control group who were fed oatmeal and cracked wheat. The increased rate of gain in the group of children fed the special cereal mixture as compared with that in the control group was marked for the first three months of the observation. During the second three months the gain in weight of the group receiving the special cereal, although somewhat slower, was greater than that shown by the control group during the same period. The observations are being continued for another six months in order to obtain further information on this point.

The gain in weight of the children fed the special cereal cannot be due entirely to its vitamin B content. What other factors in the special cereal mixture not present in ordinary cereal are responsible for the greater gain in weight of this group is not clear. It is possible that the rich mineral content or the increased ease of digestibility of the cereal mixture [4] may be of significance.

CONCLUSIONS

The addition of vitamin B to a good diet fed to normal children produced an increase in weight 1.6 times the expected increase over a period of six months.

The substitution of 3 ounces of a special cereal mixture rich in vitamin B and various mineral elements for 3 ounces of ordinary cereals in the diet of normal children produced an increase in weight 2.3 times the expected gain over a period of six months.

The increased rate of gain obtained when the special cereal is substituted for ordinary cereals is not entirely due to its high vitamin B content.

A group of normal children fed a good diet showed an increase in hemoglobin content during the six month period of observation from 10.4 to 10.7 Gm. per hundred cubic centimeters of blood. When a vitamin B concentrate free from iron and copper was added to the diet the hemoglobin increased from 10.1 to 11 Gm. When the cereals ordinarily consumed were replaced by the special cereal mixture the hemoglobin increased during the same period from 10.2 to 12 Gm.

4. Ross, J. R., and Burrill, L. M.: J. Pediat. **4**:654 (May) 1934.

REDUCTION OF METHYLENE BLUE BY THE BLOOD OF YOUNG INFANTS

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The constituents of the blood of infants show significant alterations during the early months of life. Most pronounced, perhaps, is the drop in hemoglobin and red blood cells. Another hitherto unrecognized feature, apparently characteristic of this period, is the rapidity with which the blood decolorizes methylene blue.

This study developed from the observation that the blood of some persons possessed the faculty of decolorizing a weak solution of methylene blue dissolved in sodium citrate, whereas the blood of other persons, under the same well defined experimental conditions, lacked this feature. Further investigation revealed that age played a dominant rôle in this phenomenon, and that a number of intrinsic and extraneous variables influenced the rapidity and intensity of the reaction.

METHOD

The method employed in this investigation was as follows: A stock solution was prepared by dissolving 200 mg. of methylene blue, U. S. P. medicinal, in 40 cc. of 3 per cent chemically pure sodium citrate. After filtration, 0.07 cc. of this solution was dissolved in 50 cc. of sodium citrate of the same strength, giving a final concentration of methylene blue of approximately 1:140,000. These solutions were kept in an icebox. To produce the most consistent results, the diluted methylene blue solution was let stand for at least twenty-four hours before use. Doubly distilled water was employed throughout. For a single test, four tubes, measuring 1 by 8 cm., were set in a rack. In each tube was placed 0.1 cc. of the diluted methylene blue solution. Blood was withdrawn from the heel in young infants and from the finger in older persons by means of a 0.1 cc. calibrated blood pipet graduated in 0.01 cc. In the younger group the quantities of blood used were 0.02, 0.03, 0.04 and 0.05 cc., respectively, and in the older group they ranged from 0.03 to 0.06 cc. With the latter, 0.1 cc. of blood was occasionally added to a fifth tube. The tubes were corked and gently agitated to secure thorough admixture, and the rack was placed in a water bath for one hour at a temperature of 15 C. Then, after centrifugation of the contents at a moderate speed for two minutes, readings were made against a white background. The degrees of reduction noted in the supernatant fluid were designated as 0 when the only change in color of the dye was dilution by the added plasma to 4 plus, in which case the dye was completely reduced, with a resulting clarity, often like that of water. The presence of traces of bile, as in jaundice of the new-born, or of other pig-

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ments did not interfere with the readings. After the extent of reduction was recorded, the tubes were placed in the icebox (from 5 to 6 C.), and were reexamined for further changes at the end of twenty-four hours.

Whenever possible, a specimen of blood was examined for hemoglobin at the time of the tests. Hellige hemometer tubes, previously standardized by an oxygen capacity method,[1] were used, and the amount of hemoglobin was determined directly in grams. In some instances, also, hematocrit determinations of cell volume were carried out. A Van Allen tube was employed,[2] since only small quantities of blood are necessary with this method.

The subjects included in this study were observed in the wards and in the outpatient department of the Children's Clinic of the New York Hospital.[3]

RESULTS

The results are considered under the heading of the particular factor which influenced some phase of the reaction.

Age.—In table 1 are summarized the results of more than six hundred tests of the blood of two hundred and thirty-eight healthy persons,

TABLE 1.—*Reduction of Methylene Blue by the Blood of Young Infants*

Age	Number of Subjects	Degree of Decolorization*					Number of Observations
		0	1	2	3	4	
0–1 mo.	54	0.9†	5.7	4.8	21.1	67.3	104
1–4 mos.	134	0.0	1.4	4.3	7.3	86.8	205
4–8 mos.	105	33.8	19.0	16.5	13.2	17.3	121
8 mos.–1 yr.	63	59.7	22.2	12.5	5.5	0.0	72
1–40 yrs.	92	86.6	10.2	2.3	0.7	0.0	127

* The degrees of decolorization range from 0, with no reduction, to 4 plus, when decolorization of the dye is complete. The plus designation has been omitted in the tables, and the values are noted simply as 0, 1, 2, 3 and 4. In this table alone, each value represents the average, approximately, of the degrees of reduction observed in the tubes containing 0.04 and 0.05 cc. of blood, respectively. The degrees of decolorization are designated in the same way in each table.

† The numbers represent percentages of the total observations in each age group.

when the readings were made after an incubation period of one hour. Two thirds of the tests were performed with specimens of blood obtained from subjects in the youngest age groups. Typical examples of individual cases are presented in table 2. It is obvious from both tables that the capacity to reduce methylene blue was most intense during the first four months of life. From this point, the velocity of reduction gradually diminished, and by the end of the first year it was indistinguishable from that in the older child and adult.

1. Sendroy, J. Jr.: Manometric Determination of Hemoglobin by the Oxygen Capacity Method, J. Biol. Chem. **91**:307 (April) 1931.

2. Van Allen, C. M.: Hematocrit Method, J. Lab. & Clin. Med. **10**:1027 (Sept.) 1925.

3. The follow-up of the infants in the latter group was carried out with the cooperation of Miss Elizabeth Rogers and Miss Alcida Coulter of the nursing staff.

The tables also reveal the decreased reducing capacity of the blood of some infants during the first month of life, as compared with the three succeeding months. That bile pigments in the blood of infants with jaundice of the new-born are not responsible for the diminished reaction is shown by instances in which icterus persisted beyond the first month of life, and in which the dye was completely reduced (table 5).

In the entire group of infants studied, the blood of premature babies presented the feature of decolorizing the methylene blue solution most rapidly and completely. In an occasional instance, decolorization was carried on beyond 1 year of age.

TABLE 2.—*Typical Cases Illustrating Reduction of Methylene Blue by Blood of Infants*

Subject	Age	Degrees of Decolorization Blood, Cc. 0.03	0.04	0.05	Hemoglobin
R. H.	27 days	3	4	4	....
	6 weeks	4	4	4	....
	2 mos.	3	4	4	....
	3½ mos.	2	4	4	12.4
	4 mos.	1	4	4	....
	5 mos.	1	2	2	11.8
	6 mos.	0	0	0	12.2
A. M. K.	2 mos.	2	4	4	10.4
	3½ mos.	2	4	4	13.0
	4½ mos.	0	2	3	13.0
	5½ mos.	0	0	0	12.2
De P.	2 mos.	2	4	4	11.0
	3¾ mos.	0	3	3	12.0
	4¾ mos.	0	1	2	12.0
	6 mos.	0	0	1	11.8
	8 mos.	0	0	0	12.6
L. B.	2½ mos.	3	4	4	13.2
	4 mos.	1	4	4	12.4
	6 mos.	1	2	3	12.8
	7 mos.	0	1	1	10.2
	8 mos.	0	0	0	11.2

The decolorization phenomenon was studied in the young of another species. The blood of three young rabbits was examined periodically. The results (table 3) corresponded to the observations made in the human infant, except that the reducing power in the rabbit disappeared earlier in life, usually between 2 and 3 months of age. In a limited number of observations, it was noted that methylene blue was also decolorized by the blood of the young guinea-pig and rat, and that in these animals this property was diminished during the second month of life. The dye was not decolorized as strongly, however, by the young of these animals as by the blood of the human infant and rabbit of corresponding ages.

Temperature.—The effect of temperature on decolorization became evident in the course of the experiments. It was soon observed that decolorization took place most readily in a cold temperature, and more

slowly at body temperature. The dye was not decolorized at 2 C. The optimum temperature range appeared to lie between 10 and 20 C., with 15 C. as most favorable. At 37 C., not only was the reaction less marked than at 15 C., but it was often confused by hemolysis. In the icebox, decolorization persisted indefinitely. Return of the blue color to the supernatant layer was effected only in the warmth.

P_H of the Medium.—Reduction of methylene blue by the blood of the young baby took place only when the dye had been added to sodium citrate with a definite hydrogen ion concentration. Reduction occurred readily, either in the unbuffered solution at p_H 8.1, or in solutions of citrate buffered with phosphates producing a p_H of 7.4 and 8.1. In a more acid solution, p_H 6.3, the dye was not decolorized.

TABLE 3.—*Examples of Reduction of Methylene Blue by the Blood of Rabbits*

		Degrees of Decolorization Blood, Cc.			
Rabbit	Age	0.03	0.04	0.05	Hemoglobin
X 1	1 mo.	4	4	4	....
	7 weeks	4	4	4	10.2
	2 mos.	2	3	4	11.8
	3 mos.	0	0	0	14.2
	4 mos.	0	0	0	14.0
F 3	2 days	2	4	4	....
	10 days	3	4	4	....
	1 mo.	2	4	4	....
	7 weeks	1	4	4	....
	10 weeks	0	0	0	....
	3 mos.	0	0	0	....

Dilution of Methylene Blue.—The blood of eight infants, ranging in age from 22 days to 5 months, was added to the ordinary solution of methylene blue (1 : 140,000) and the reaction compared with that when a more concentrated solution of the dye (1 : 50,000) was used. It was observed, after one hour of incubation, that little or no decolorization occurred in the strong solution, in striking contrast to the marked reduction in the more diluted solution. The influence of this factor, as well as of temperature and hydrogen ion concentration of the medium, may be observed in illustrative cases in table 4.

Oxygen.—In order to determine the rôle of the column of air above the mixture of blood in the tube, the blood in several instances was permitted to enter the methylene blue solution under a layer of oil. Reduction in a few instances was less intense than when the blood was exposed directly to the column of air in the tube, but the difference was not sufficiently striking to lead to the conclusion that the reaction depends in any way on the oxygen outside of the mixture. In blood possessing strong decolorizing properties, the reaction was unaffected by the exclusion of air.

The clear supernatant fluid was removed after decolorization, and oxidation was attempted by vigorous shaking with air and also after the addition of strong oxidizing reagents, such as hydrogen dioxide, potassium permanganate and nitric acid. In no instance, after a large number of trials, was the original blue color of methylene blue restored.

Constituents of the Blood.—The element of the blood responsible for the reaction appears to reside in the red cell. The serum was removed from the clot, and varying quantities were added to the solution

TABLE 4.—*Cases Illustrating Influence of Various Factors on the Reduction of Methylene Blue*

		Blood, Cc.											
		0.03	0.04	0.05	0.03	0.04	0.05	0.03	0.04	0.05	0.03	0.04	0.05
		Concentration of Methylene Blue											
Subject	Age	1:140,000			1:50,000								
Baby F	1½ mos.	4	4	4	0	0	1						
Baby R	1¾ mos.	1	4	4	0	0	0						
Baby C	2 mos.	4	4	4	0	0	1						
Rabbit Z 1	1 mo.	3	4	4	0	1	1						
		Temperature											
		2 C.			15-20 C.			37 C.					
Baby R	1½ mos.	..	..	..	1	4	4	0	1	1			
Baby G	2 mos.	0	0	0	1	3	4	0	1	2			
Baby F	2 mos.	0	0	0	3	4	4	2	3	4			
Rabbit X 2	2 mos.	..	..	..	3	4	4	0	2	2			
		p_H of Medium											
		Phosphate Buffers Added									Not Added		
		6.3			7.4			8.1			8.1		
Baby C	22 days	0	0	2	4	4	4	0	3	4	4	4	4
Baby Q	7 wks.	0	0	0	1	4	4	0	2	3	3	4	4
Baby D	10 wks.	0	0	0	2	4	4	2	3	4	3	4	4
Rabbit X 1	2 mos.	0	0	0	2	3	4	..	..	..	2	3	4

of metheylene blue. No reduction occurred, even after twenty-four hours in the icebox. The blood of three adults with diabetes and marked hyperglycemia did not reduce the dye within the one hour period of the test. The influence of previous ingestion of food was further eliminated when it was observed that the blood of a month old rabbit, starved for twenty-four hours, reduced the dye completely and rapidly. The plasma obtained from citrated blood similarly showed no reaction to the dye. When citrated blood was permitted to stand at 15 C., the clear supernatant layer contained practically a pure suspension of platelets. The solutions of methylene blue were not reduced by the addition of varying proportions of the suspension.

Leukocytes as a factor were investigated directly and indirectly. The buffy coat containing the white blood cells was removed after centrifugation with the least possible contamination by adhering red blood

cells and mixed with small quantities of methylene blue. No reduction occurred. The blood of three children with lymphatic leukemia, in one instance with 135,000 white blood cells, was mixed with the methylene blue according to the conditions of the experiment. No decolorization took place, even after twenty-four hours. The blood of these subjects was of particular significance since it was associated with severe grades of anemia, and represented, in effect, suspensions of white blood cells. In other children with marked leukocytosis and a high proportion of polymorphonuclear neutrophils, no changes appeared in the dye, as observed after the one hour incubation period.

More direct evidence pointed to the erythrocytes as the basic factor in the blood in the decolorization process. When centrifugation was done at low speed for a short period and the cells were washed, reduction was effected, but only when a 50 per cent suspension of cells was added to the methylene blue. The reaction did not occur with the same velocity as when whole blood was used, but was often delayed for several hours. Centrifugation interfered with the decolorization reaction.

That the erythrocyte or one of its constituents, such as hemoglobin, is the effective agent in reducing the methylene blue solution was indicated by oxidizing hemoglobin to methemoglobin. The addition of a trace of sodium nitrate to the mixture of blood and dye produced methemoglobin without laking the blood and interfered with the decolorization reaction. The formation of methemoglobin was observed spectroscopically in the characteristic appearance of the bands. In the tubes containing blood and solution of methylene blue alone, as in the test, methemoglobin was not formed. The bands observed spectroscopically were those of oxyhemoglobin.

The cellular sediment, after exposure to the dye, was washed three times in a saline solution. Microscopic examination, after the last washing, with fixed and supravital technics revealed that the centrifugated layer was composed almost entirely of red cells. The erythrocytes appeared to be normal, without any evidences to indicate they had adsorbed the dye. After the addition of 0.1 cc. of dye-free sodium citrate to the washed cells at 37 C., a blue color developed in the supernatant layer within an hour. The color developed more slowly and its intensity was less if saline solution was substituted for the dye-free sodium citrate solution. These observations suggest not only that the dye was withdrawn by the erythrocytes but that it was reduced.

It was also noted that the centrifugated cells of the young infant decolorized fresh additions of methylene blue. The clear supernatant layer was removed and 0.1 cc. of methylene blue was again added to the several tubes. After incubation for one hour in the cold, the dye was again reduced. In most instances, it was necessary to allow the mixture to stand for a variable length of time, up to twenty-four hours, in the

icebox. The blood of several young infants decolorized two fresh additions of methylene blue after the original test. This reduction was always in contrast to the failure of the blood of older infants, children and adults to decolorize repeated additions of the dye.

The lack of correlation between the amount of hemoglobin and the cell volume, as determined by the hematocrit and the extent of reduction, is illustrated in several cases in table 5. It is also evident from tables 2 and 3 that no quantitative relationship existed between hemoglobin

TABLE 5.—*Reduction of Methylene Blue by Infants and Relationship of Hemoglobin, Cell Volume and Icterus*

Subject	Age	Degrees of Decolorization Blood, Cc. 0.03	0.04	0.05	Hemoglobin, Gm.	Cell Volume, per Cent	Plasma Icteric
W. T.	6 hours	0	4	4	....	60	+
	8 days	0	1	4	....	46	+
	3 weeks	3	4	4	....	30	0
	2½ months	4	4	4	11.4	..	0
	3 mos., 3 wks.	2	2	3	11.6	..	0
	4 mos., 3 wks.	1	2	3	11.8	..	0
	5 mos., 3 wks.	0	1	1	11.2	..	0
B. N.	6 hours	0	4	4	....	..	+
	9 days	0	2	4	....	66	+
	15 days	1	2	4	....	41	+
	18 days	0	4	4	....	45	+
	22 days	2	4	4	....	..	+
D. Q.	1 month	4	4	4	15.3	..	+
	7 weeks	4	4	4	11.9	..	+
	2 months	3	4	4	....	..	+
	3 months	2	4	4	....	..	0
	4 months	0	3	4	....	..	0
	5½ months	0	3	3	12.2	..	0
	6 months	0	2	2	15.0	..	0
	7½ months	0	0	0	14.5	..	0
R. P.	9 days	0	0	0	....	..	+
	12 days	0	2	4	....	55	+
	14 days	0	0	4	....	56	+
	16 days	1	4	4	....	53	+
	20 days	0	4	4	....	43	+
	3 months	1	3	4	....	..	0
	6 months	0	0	0	....	..	0

values alone and the degree of decolorization. Directly after birth, when the hemoglobin value was highest, the reduction of methylene blue was less pronounced than in the weeks that followed. It was evident, however, during this investigation, that a minimum hemoglobin and cellular content were essential for the reaction. Table 5 also shows that the presence of icterus did not interfere with the completeness of reduction, but rather that some other factor in the red cell was responsible for the decreased decolorization during this period.

Youth of the red cells played no part in the decolorization process. This seemed apparent from the failure of the erythrocytes in many instances to decolorize methylene blue directly after birth, when nucleated and reticulated red cells were normally most common. The blood of a young infant of 6 months with a blood picture of pernicious anemia and of several children with von Jaksch's anemia, all with many normo-

blasts in the smear, showed no reduction of the dye. The blood of an adult patient with pernicious anemia which contained more than 20 per cent reticulocytes after liver therapy did not decolorize the solution of methylene blue.

Delayed Reduction.—When the blood of an older infant, child or adult which produced no decolorization in one hour was permitted to stand in the icebox for twenty-four hours after centrifugation, the dye was reduced in some degree in the large majority of instances, particularly in the tubes containing the larger quantities of blood. In contradistinction to the primary rapid reduction by the blood of young infants, this result was designated as the delayed reduction reaction.

Effect of Illness.—During the course of the investigation, it was noted that supervening illness of variable severity usually interfered with the primary decolorization reaction in the young infant. It was subsequently observed that when the blood of the older person was set aside in the icebox for later reading, the delayed reaction also failed to appear in the event of illness. Studies are now in progress which concern the possible clinical pathologic implications of this observation.

COMMENT

These studies suggest that the red blood cells of the young infant possess the property of reacting to methylene blue, and that this is modified during growth. The actual mechanism by which decolorization is effected can only be conjectured. Some of the features of the reaction resemble established physiologic and physicochemical phenomena.

It is necessary at first to consider some of the properties of methylene blue. It is a quinoid dyestuff, tetramethyl thionine, which probably always occurs in association with its products of oxidation, such as the azures, and in alkaline medium with methylene violet.[4] To what extent these products are formed at the p_H of these experiments is unknown, but it is conceivable that they account for the slight differences in reactions that are sometimes noted when new solutions are made up. Irwin[5] recently presented evidence that methylene blue does not penetrate the living cell as such, but in the form of a product of oxidation, trimethyl thionine, or azure B.

Methylene blue contains no oxygen in its molecule, and is reduced to a colorless or leuko-compound when its chromophore groupings combine with hydrogen. Methylene blue loses its color, therefore, by reduc-

4. Holmes, W. C.: The Oxidation Products of Methylene Blue, Stain Technology **1**:17 (Jan.) 1926.

5. Irwin, M.: Nature of Dye Penetrating Vacuole of Valonia from Solutions of Methylene Blue, J. Gen. Physiol. **10**:927 (July) 1927.

tion, and regains it by oxidation, and it is by virtue of these changes that it is often employed as an indicator in the study of biologic oxidations.

The oxidation-reduction system of Wieland and Thunberg,[6] as applied to cellular metabolism, involves a group of enzymes known as dehydrogenases, which possess the power of activating the oxidation of certain organic substances. In this process, according to their conception, the hydrogen of the substances to be oxidized is activated, and when the methylene blue is available, the dye is reduced to a colorless compound. By the Thunberg technic,[6a] experiments in cell metabolism were carried out under anaerobic conditions, since any oxygen present caused the hydrogen liberated in oxidation of tissue to form water instead of to reduce methylene blue. He regarded the time of decoloration of the methylene blue as a measure of the activity of the system. In the present studies, since oxygen is poorly dissolved in the cold, the reduction of methylene blue proceeded without interference. Little difference was noted whether or not the admixture of the blood and methylene blue was superimposed by a layer of oil or by a column of air.

The existence of enzymes or dehydrogenases in plant and animal tissues capable of oxidizing citric acid and citrates was pointed out by Thunberg [7] and Bernheim.[8] It is conceivable that the erythrocytes possess a dehydrogenase of this type which reduces methylene blue in the presence of sodium citrate. It is necessary to assume that this enzyme is present in largest quantity in the blood of young infants and diminishes with advancing age. Citric acid occurs as a normal constituent of human and cow's milk.[9] In his table in which the citric acid content of various fluids is mentioned, Thunberg [6a] included the observations of Jerlov, who showed that citric acid does not appear in women's milk until two days after delivery. The blood of four women was studied in the present investigation during the first postpartum day, and again four days later. Reduction did not occur within the one hour incubation period, and slight degrees of decolorization occurred after twenty-four hours at icebox temperature in all the specimens. However, the dye was most rapidly decolorized during the early months of the infant's life, when milk was the exclusive article of diet.

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6. (*a*) Thunberg, T.: The Hydrogen-Activating Enzymes of the Cells, Quart. Rev. Biol. **5**:318 (Sept.) 1930. (*b*) Dixon, M.: Oxidation Mechanisms in Animal Tissues, Biol. Rev. **4**:352 (Oct.) 1929.

7. (*a*) Thunberg, T.: Ueber eine Citrico-dehydrogenase in Gurkensamenextrakt, Skandinav. Arch. f. Physiol. **55**:280, 1929; (*b*) footnote 6a.

8. Bernheim, F.: The Specificity of the Dehydrases; Separation of the Citric Acid Dehydrase from Liver and of the Lactic Acid Dehydrase from Yeast, Biochem. J. **22**:1178, 1928.

9. Allen, L. A.: The Mineral Constituents and Citric Acid Content of Milk, J. Dairy Research **3**:1 (Dec.) 1931.

In the absence of quantitative measurements of the sodium citrate content of the tube before and after incubation of the blood and dye, the explanation of the reaction by the presence of a citric acid enzyme is based on inference only. There are features which are opposed to the presence of this enzyme. It has been pointed out that dye was reduced only in a cold temperature, and that the color was restored by exposure to a temperature of 37 C. In common with the characteristics of other enzymes, previous investigations bearing on the citric acid dehydrogenases indicate that the optimum temperature in this instance also approximates that of the human body. This point was borne out further when crushed cucumber seeds, which Thunberg [7a] found contain a rich supply of citric acid dehydrogenase, were substituted for blood in a mixture of methylene blue and sodium citrate. Decoloration proceeded through a wide temperature range, but most rapidly at 37 C. Again, it is necessary to assume the universal presence of at least traces of this enzyme, since the blood of all healthy subjects decolorizes the dye at some time following the initial one hour incubation period.

Another mechanism which may underlie the phenomenon described is one involving the intracellular oxidation and reduction of glutathione. This substance is widely distributed in animal tissues, and possesses the property of being oxidized or reduced under favorable conditions within the cells. In the blood, glutathione resides in the erythrocytes and exists there mainly in its reduced form.[10] The periods of most rapid growth in plants and animals have been associated with increased amounts of glutathione in their tissues. In ten instances, Anselmino and Hoffman [11] found that the glutathione content was on the average 40 per cent higher in the blood of the umbilical cord than in the blood of the mother, and that this was unrelated to hemoglobin values. Thompson and Voegtlin [12] showed that in the albino rat the total glutathione of the whole body declines with advancing age. According to this conception, when the larger quantities of glutathione present in the red cells of the actively growing and developing organism undergo oxidation, methylene blue may be simultaneously and rapidly reduced to its leuko-derivative. The readiness with which glutathione is oxidized in a neutral or slightly alkaline medium is analogous to the rapidity with which methylene blue is reduced by the blood of young infants in a solution of comparable reaction.

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10. Meldrum, N. U.: Reduction of Glutathione in Mammalian Erythrocytes, Biochem. J. **26**:817, 1932.

11. Anselmino, K. J., and Hoffman, F.: Ueber den Glutathion- und Katalasegehalt des fetalen Blutes und seine Bedeutung für die Sauerstoffversorgung der Frucht, Arch. f. Gynäk. **143**:505, 1931.

12. Thompson, J. W., and Voegtlin, C.: Glutathione Content of Normal Animals, J. Biol. Chem. **70**:793 (Nov.) 1926.

Methylene blue serves not alone as a passive indicator of biologic oxidations, but as an active respiratory catalyst. Harrop and Barron,[13] among others, showed that non-nucleated, adult mammalian erythrocytes possess a very small oxygen consumption. They showed that when methylene blue in low concentration was added, the amount of oxygen absorbed was enormously increased, reaching the highest levels at a temperature of 37 C. Their hypothesis is, therefore, that methylene blue serves as an oxygen-activating catalyst and restores a substance to the non-nucleated erythrocytes, enabling them to carry on respiration comparable to that of the nucleated red cells of avian blood. Warburg, Kubowitz and Christian [14] pointed out that methylene blue catalysis in red blood cells involves stages in which hemoglobin is oxidized to methemoglobin, and in which the resulting leuko-compound is subsequently oxidized to the original dye. Wendel [15] also observed that methemoglobin was formed in the erythrocytes of the dog in the course of the oxidation of lactic acid in the presence of methylene blue. He noted the appearance of the characteristic absorption band of methemoglobin in the course of these experiments.

These investigations are cited to indicate that the conversion of hemoglobin to methemoglobin constitutes one of the phases of the catalysis of methylene blue. As far back as 1891, Combemale [16] noted the presence of methemoglobin in the blood of dogs after the injection of methylene blue. However, Williams and Challis,[17] in a recent study, could not duplicate these results with rabbits. It is noteworthy that numerous spectroscopic examinations of the mixtures of methylene blue in the blood were carried out in the present study after various intervals of incubation, which did not at any time reveal the absorption band characteristic of methemoglobin. It is possible that such minute traces of methemoglobin are formed that they cannot be detected with this method. Confirming the likelihood that methemoglobin was not formed

13. Harrop, G. A., Jr., and Barron, E. S. G.: Studies on Blood Cell Metabolism: Effect of Methylene Blue and Other Dyes on the Oxygen Consumption of Mammalian and Avian Erythrocytes, J. Exper. Med. **48**:207 (Aug.) 1928.

14. Warburg, O.; Kubowitz, F., and Christian, W.: Kohlenhydratverbrennung durch Methämoglobin: Ueber den Mechanismus einer Methylenblaukatalyse, Biochem. Ztschr. **221**:494, 1930; Ueber die katalytische Wirkung von Methylenblau in lebenden Zellen, ibid. **227**:245, 1930.

15. Wendel, W. M.: Oxidations by Erythrocytes and the Catalytic Influence of Methylene Blue, J. Biol. Chem. **102**:373 (Oct.) 1933.

16. Combemale, M.: De l'action méthémoglobinisante du bleu de méthylène, Compt. rend. Soc. de biol. **43**:300, 1891.

17. Williams, J. R., and Challis, F. E.: Methylene Blue as an Antidote for Anilin Dye Poisoning, J. Lab. & Clin. Med. **19**:166 (Nov.) 1933.

is the observation of Brooks [18] that hemoglobin is oxidized to methemoglobin in more acid solutions, and at a temperature of 25 C., as compared with 15 C.

In the observations on the mixture of the blood and dye, it was pointed out that the colorless layer of fluid superimposed on the sedimented layer of cells after incubation could not be oxidized to the original blue color chemically, or by vigorous shaking. That the dye was associated with the cellular layer was apparent. Washing of this sediment several times did not prevent the development of the blue color when saline that was free from dye or citrate was added, and the mixture incubated at 37 C. The absence of leuko-dye in the supernatant layer after the primary incubation period suggested the adsorption of the dye from the solution by the cellular elements. Methylene blue dissolved in sodium citrate probably exists in a colloidal state, and obeys the physicochemical laws relating to adsorption. Bayliss [19] pointed out that electrolytes influence the behavior of dyes in colloidal solution during the process of adsorption. He observed that when the same amount of filter paper was exposed to progressively diminished concentrations of solutions of dye, such as congo red, the dye was taken up in larger proportions, the more dilute the solution. In the reaction of blood to different concentrations of methylene blue (1 : 50,000, as compared with 1 : 140,000), it seems likely that the red blood cells obeyed this "law of adsorption." It is conceivable that the rapidity of decolorization of methylene blue solutions depends on an inherent facility of the red cells of the young infant to adsorb the dye on their surface. In dilute solutions of the dye, of a concentration of 1 : 140,000, this capacity became manifest by inspection. Possibly the extraction of the colloidal particles of the dye from the solution by the erythrocytes was aided by the presence of sodium citrate or a product of its dissociation.

In confirmation of the observations of Bayliss are the studies of Iwanowsky and Sabolotnowa,[20] who investigated the adsorption of methylene blue by the erythrocytes of rabbits. Without considering the age of the animals, they found that the red blood cells adsorbed a maximum amount of dye from a solution of sodium chloride at the end of thirty minutes. The largest relative percentage of the amount originally in the solution was withdrawn by the cells in the weakest concentrations of dye. Very little of the adsorbed dye was released by the

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18. Brooks, J.: The Oxidation of Haemoglobin to Methaemoglobin by Oxygen, Proc. Roy. Soc., London, s.B **109**:35 (Sept. 1) 1931.

19. Bayliss, W. M.: Aspects of Adsorption Phenomena, Biochem. J. **1**:175, 1906.

20. Iwanowsky, N., and Sabolotnowa, M.: Ueber die Adsorptionsfähigkeit der Erythrocyten; Adsorption von Methylenblau, Biochem. Ztschr. **216**:130, 1929.

red cells, despite as many as ten washings with saline solution. It is interesting that in the present study the methylene blue appeared in greater concentration in the supernatant layer when the erythrocytes previously exposed to the dye were later incubated at 37 C. with a solution of sodium citrate, rather than with saline solution.

The adsorptive properties of red blood cells have been determined for substances other than dyes. The selective adsorption of diphtheria toxin by erythrocytes after in vitro admixture, or following intravenous injection, has been established.[21] An attempt to apply this observation to the interpretation of susceptibility to diphtheria has been the subject of controversy.[22] The relationship of the age of the subject, from the standpoint of adsorption of toxin by the red cells, has not yet been investigated. It is possible that the increased adsorption of dye by the erythrocytes of the young infant or animal may find its application in immunologic phenomena peculiar to this age period.

The diminished capacity for decoloration of the red cells during the first weeks of life in a large number of the subjects studied (table 1), as compared with the later months, cannot be satisfactorily explained. This difference was particularly pronounced during the period of the deepest jaundice. As pointed out, however, complete reduction of methylene blue occurred in some infants beyond the first month, in spite of the presence of icterus. It is possible that the postnatal hemolytic process is responsible for the production of cellular products, other than bile pigments, which interfere with the reaction. The length of time during which decolorization is impaired may depend on the duration and intensity of the hemolytic process, together with the efficiency with which the liver of the newly born infant can dispose of the products formed.

Van Creveld [23] found that the mean diameter of the red blood cells was greatest in the first four weeks of life in the full term baby, and in the first two weeks in the premature baby. This was the period during which the hematocrit readings and hemoglobin reached their highest values. Since these observations apply to the time when decolorization is not as pronounced as in the succeeding months, it seems plausible that the reduction of methylene blue by the erythrocytes depends on a factor unrelated to either their size or the hemoglobin content.

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21. Dujarric de la Rivière, R., and Kossovitch, N.: Globules rouges et immunité; adsorption des toxines par les globules rouges, Compt. rend. Soc. de biol. **110**:284 (June 3) 1932.

22. Glausmann, M. P.: Ueber die Adsorptionsfähigkeit der Erythrocyten und die Diphtherie Immunität, Biochem. Ztschr. **177**:309, 1926.

23. van Creveld, S.: Diameter of Red Blood Cells of Premature Infants and of Those Born at Full Term, Am. J. Dis. Child. **44**:701 (Oct.) 1932.

The affinity of the erythrocytes for dye was altered by centrifugation and washing of the red blood cells. Barron and Harrop [24] emphasized the importance of the integrity of the erythrocytes for normal glycolysis and action of methylene blue. The use of whole blood subjected to a minimum of trauma, as carried out in the present studies, constituted a factor of basic importance in demonstrating the selective ability of the erythrocytes of the young to adsorb large quantities of methylene blue. Preliminary defibrination or centrifugation apparently caused sufficient damage to the corpuscular surface of erythrocytes to impair their adsorptive capacity. Observations now in progress on the blood of sick children indicate that the disturbance of normal physiologic processes in disease can also manifest itself by interfering with the decoloration properties of the red blood cell.

Experiments such as those of Morawitz [25] to show the increased metabolism of young red blood cells in experimental anemia are not related to the reaction under consideration. The blood of anemic persons produced either slight or no reduction of methylene blue, even after twenty-four hours of incubation. Instances of marked reticulation of the erythrocytes were not accompanied by evidences of increased reduction of the dye. It seems, rather, that the erythrocytes of the young infant pass through a stage of development in which they manifest increased capacities to adsorb methylene blue.

In summary, the reaction described cannot as yet be completely accounted for on the basis of any well known physiologic law. It must be remembered, however, that the nature of the conditions prescribed by the technic probably introduces experimental factors which render precise conformance to established principles an impossibility. Analysis of the properties that have been commented on indicates that they may contribute to a twofold reaction. The first stage consists of adsorption of the dye by the erythrocytes, a process which is probably regulated by precise physicochemical laws. In the second stage, the adsorbed dye is reduced to a colorless compound. This phase is related to any one or a combination of oxidation-reduction mechanisms known to operate in the tissues. Of these, the most likely appears to be the activity of an enzyme, such as citric acid dehydrogenase, or reduction through the medium of the glutathione system.

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24. Barron, E. S. G., and Harrop, G. A., Jr.: Studies on Blood Cell Metabolism; Effect of Methylene Blue and Other Dyes on Glycolysis and Lactic Acid Formation of Mammalian and Avian Erythrocytes, J. Biol. Chem. **79**:65 (Sept.) 1928.

25. Morawitz, P.: Ueber Oxydationsprozesse im Blut, Arch. f. exper. Path. u. Pharmakol. **60**:298, 1909.

SUMMARY

1. The blood of the young infant possesses the property of decolorizing methylene blue rapidly.

2. The decolorization of a dilute solution (1 : 140,000) of methylene blue in 3 per cent sodium citrate was studied in the blood of two hundred and thirty-eight healthy subjects of various ages according to a standardized technic. In more than six hundred tests, the dye was most rapidly and completely reduced during the first four months of life. During the remainder of the first year, the blood gradually assumed the less pronounced decolorizing capacity of the adult.

3. The blood of three young rabbits, examined periodically, exhibited a maximum reduction of the dye during the first two months of life. In a limited number of tests it was noted that the blood of the guinea-pig and rat revealed a similar property during the first month of life, although its activity was less pronounced than in the human infant or in the rabbit.

4. Decolorization proceeded most rapidly at a p_H of 7.4 and 8.1, and was interfered with in a more acid medium of p_H 6.3. The optimum temperature range for the reaction was from 10 to 20 C., with 15 C. the most favorable.

5. The element of the blood responsible for the reaction resides in the erythrocyte. No quantitative relationship, however, exists between the hemoglobin and hematocrit values and the degree of decolorization.

6. Youth of the red cells, as indicated by reticulation and nucleation, played no part in the reaction. This observation seems further confirmed by the less intense reduction of the blood in the first week or two of life.

7. Many of the phases of the reaction suggest a relationship to the phenomenon of adsorption. It would appear that the erythrocytes of the young infant during the first four months of life pass through a stage of development in which they manifest increased capacities to adsorb methylene blue.

8. It is possible that the activity of an enzyme, such as a citric acid dehydrogenase, or reduction through the medium of the gluthathione system may also play a part in the reaction.

9. Supervening illness interfered in many instances with the rapid adsorption of the dye by the blood of the young infant. More commonly, illness retarded the delayed reduction normally observed in the blood of older children and adults.

10. The increased adsorption of dye by the erythrocytes of the young infant or animal may find its application in immunologic phenomena peculiar to this age period.

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ANEMIA OF PREMATURE INFANTS

II. A COMPARATIVE STUDY OF BLOOD IRON AND HEMOGLOBIN VALUES IN PREMATURE INFANTS

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Determination of the iron content of the whole blood in infancy and childhood has not been extensively investigated. Gallo [1] compared blood iron values with hemoglobin values which he had obtained from healthy new-born infants and could find no direct proportion between the two. Kotikoff [2] in a study of 20 healthy full term infants determined the average values for whole blood iron for the first year of life. From a comparison of the average values for whole blood iron with the hemoglobin values obtained for another group of infants over a like age period, he concluded that in the full term infant during the first year of life the values for hemoglobin and for whole blood iron follow similar curves. From the formula percentage of hemoglobin over milligrams of iron per hundred cubic centimeters he established a constant for the two values from the new-born period to the age of 1 year. Halfer [3] studied the iron content of the whole blood of 126 infants and children, 22 being healthy infants in the first year of life. He could establish no relationship between the values for hemoglobin and those for iron, but this may have been due, as Kotikoff pointed out, to the inaccuracies inherent in the method which he employed for his iron determinations.

Sobel and Drekter [4] reported a study of the blood iron content in 135 healthy and sick children. The 48 normal children ranged from 3 to 12 years of age. The results of determinations of the blood iron in healthy young adults were recently reported by Sachs, Levine and Appelsis.[5]

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From the Premature Infant Station, Sarah Morris Hospital for Children, and the Nelson Morris Institute for Medical Research, Michael Reese Hospital. The work was aided by grants from the Infants Aid Society and the Albert B. Kuppenheimer Fund.

1. Gallo, C.: Iron in the Blood of New-Born, Pediatria **32**:606 (May 15) 1924.

2. Kotikoff, I. A.: Ueber den Eisengehalt im Blute der Säuglinge, Jahrb. f. Kinderh. **132**:180 (July) 1931.

3. Halfer, G.: Le fer dans le sang chez les enfants sains et chez les enfants malades, Arch. de méd. d. enf. **33**:659 (Nov.) 1930.

4. Sobel, I. P., and Drekter, I. J.: Determination of the Iron Content of the Blood in Children, Am. J. Dis. Child. **45**:486 (March) 1933.

5. Sachs, A.; Levine, V. E., and Appelsis, A.: Iron in Human Blood, Arch. Int. Med. **52**:366 (Sept.) 1933.

In studying the anemia of premature infants,[6] the problem of the relationship of the iron content of the whole blood to the hemoglobin content was considered worthy of investigation. The following report is based on simultaneous determinations of blood iron and hemoglobin in a group of healthy, normal premature infants from birth to 8 months of age. The reported findings are based on 108 determinations made on 58 premature infants (table 1).

EXPERIMENTAL MATERIAL

All the infants included in this study were healthy premature infants. The majority were of less than 35 weeks' gestation and weighed less than 2,000 Gm. at birth. While in the hospital they were kept in incubators in a special ward, and after discharge they were brought at regular intervals to a clinic for premature infants in the outpatient department. Routine feedings consisted of breast milk obtained from supervised wetnurses; later, skimmed and whole buttermilk, and whole milk and evaporated milk modifications were substituted. Orange juice and cod liver oil or vitamin D concentrates were added within a few weeks after birth, and cereals and vegetables were added to the diet from the fourth to the sixth month of life. A social service nurse made visits to the infants' homes after they had left the hospital, and any infant who had an illness, such as an infection of the upper respiratory tract, intestinal upset or some other acute disease, was excluded from this series. Likewise, all infants were examined serologically for congenital syphilis, and no syphilitic infant was included.

METHODS

Determination of the Whole Blood Iron.—A slight modification of the method of F. S. Fowweather[7] was employed for the determination of the iron in the blood. After the heel of the infant had been lanced so that a free flow of blood was obtained, 0.2 cc. of blood was drawn into a pipet and rapidly emptied into a 50 cc. calibrated pyrex test tube. The pipet was rinsed with as little water as possible, and care was taken that the blood did not clot. To the blood in the test tube was added 1 cc. of concentrated sulphuric acid. The test tube was set in a holder at an angle of 40 degrees, and the contents were boiled until white fumes were evolved. After one minute of cooling, 0.5 cc. of superoxol was added cautiously drop by drop, and the heating was continued until white fumes again appeared. At this point heating was discontinued, and after one minute of cooling, 0.5 cc. more of superoxol was added. Heating was continued for one minute after the solution became colorless.

The contents of the test tube were completely cooled, and 18 cc. of water was added. One cubic centimeter of a standard solution of iron containing 0.1 mg. of iron and 1 cc. of concentrated sulphuric acid was placed in another 50 cc. calibrated pyrex test tube and diluted with 18 cc. of water. Twenty-five cubic

6. Abt, Arthur F., and Nagel, Beth R.: Prophylaxis of the Anemia of Premature Infants, J. A. M. A. **98**:2270 (June 25) 1932.

7. Fowweather, F. S.: Determination of Iron in Blood, Tissues and Urine, Biochem. J. **20**:93, 1926.

TABLE 1.—*Analysis of Results of 108 Determinations of Blood Iron Made on 58 Premature Infants*

No.	Age, Days	Pregnancy, Weeks	Weight at Birth, Gm.	Weight at Time of Analysis, Gm.	Hemoglobin (Newcomer), Gm. per 100 Cc.	Hemoglobin (Newcomer), Percentage	Red Blood Cells, Millions	Color Index	Whole Blood Iron, Mg. per 100 Cc. (Fowweather)	Iron Calculated from Determined Hemoglobin, Mg. per 100 Cc. (Butterfield Factor)	Hemoglobin-Iron Ratio*
1	4 hours	32	1,730	1,730	21.0	124.3	5.2	1.15	66.0	71.4	1.8
2	7 hours	27	1,115	1,115	16.9	100.0	5.2	0.96	54.3	57.4	1.8
3	17 hours	32	1,830	1,830	16.8	98.0	5.1	0.96	50.0	57.1	1.9
4	2	36	1,605	1,515	23.3	138.0	5.2	1.32	80.0	79.2	1.7
5	2	30	2,115	1,995	16.9	100.0	5.2	0.96	54.3	57.4	1.8
6	4	..	1,875	1,830	21.0	124.0	5.2	1.15	60.9	71.4	2.0
7	7	32	1,730	1,675	18.0	106.0	5.1	1.03	65.7	61.2	1.6
8	7	30	2,115	2,020	18.0	106.0	5.0	1.06	68.0	61.2	1.6
9	7	..	1,930	1,805	16.8	99.0	4.7	1.05	54.3	57.1	1.8
10	7	36	2,035	1,880	21.0	124.0	4.4	1.40	65.0	71.4	1.9
11	7	34	1,630	1,490	16.2	96.0	4.8	1.00	49.5	55.5	1.9
12	9	33	1,815	1,695	23.0	136.0	5.5	1.23	73.4	78.2	1.8
13	10	34	1,650	1,625	24.0	142.0	5.4	1.31	71.4	81.6	1.9
14	11	..	1,875	1,785	19.7	116.0	4.7	1.23	62.5	66.7	1.8
15	12	35	1,590	1,590	14.9	87.0	5.3	0.82	48.0	50.6	1.8
16	14	..	1,875	1,800	19.7	116.0	4.8	1.20	56.3	66.9	2.0
17	14	32	1,240	1,140	16.8	98.0	4.7	1.11	50.0	57.1	1.9
18	14	..	1,930	1,935	16.8	99.0	4.5	1.10	55.0	57.1	1.8
19	14	36	2,035	2,210	16.2	96.0	4.5	1.06	55.5	55.0	1.7
20	16	33	1,815	1,860	21.0	124.0	5.1	1.21	71.0	71.4	1.7
21	16	34	1,630	1,610	15.3	90.0	4.4	1.02	50.0	52.0	1.8
22	17	34	1,650	1,730	21.0	124.0	5.3	1.16	71.0	71.4	1.7
23	18	36	1,553 (5 days)	1,725	14.0	83.0	5.7	0.73	59.5	47.6	1.3
24	19	35	1,590	1,740	16.9	100.0	4.7	1.06	52.0	57.4	1.9
25	21	..	1,875	1,865	15.2	90.0	4.2	1.07	56.8	51.6	1.6
26	21	33	1,815	1,990	15.2	90.0	4.7	0.95	59.5	51.6	1.5
27	21	32	1,240	1,280	17.0	100.0	4.5	1.11	52.6	57.8	1.9
28	21	36	2,035	2,150	16.2	96.0	4.2	1.14	57.1	55.0	1.6
29	21	..	1,930	2,010	15.5	92.0	4.4	1.04	57.1	52.7	1.6
30	22	34	1,650	1,820	15.0	88.8	4.5	0.98	46.2	51.0	1.9
31	23	34	1,630	1,775	15.0	88.0	4.2	1.04	54.0	51.0	1.6
32	22	36	1,605	1,580	18.0	106.0	4.6	1.15	55.5	61.2	1.9
33	24	35	1,590	1,830	14.0	83.0	4.0	1.03	54.8	47.6	1.5
34	25	36	1,553	1,890	14.5	85.0	4.6	0.92	61.5	49.3	1.3
35	26	35	1,940	2,385	19.7	116.0	4.4	1.30	54.0	66.7	1.6
36	27	36	1,850	2,090	18.0	106.0	4.4	1.20	53.1	61.2	1.9
37	27	35	1,650	1,850	15.2	90.0	4.9	0.91	57.0	51.6	1.5
38	28	35	1,590	1,950	14.0	83.0	4.0	1.03	50.0	47.6	1.6
39	28	32	1,240	1,330	16.0	94.0	4.0	1.16	64.5	54.4	1.4
40	28	37	1,975 (10 days)	2,340	15.2	90.0	4.6	0.98	49.0	51.6	1.8
41	29	36	1,605	1,725	15.7	92.0	4.2	1.09	66.6	53.3	1.4
42	30	36	2,035	2,335	15.2	90.0	4.4	1.02	50.0	51.6	1.8
43	30	36	1,553	1,975	16.2	96.0	4.6	1.04	58.9	55.5	1.6
44	31	33	1,875	2,050	14.6	86.0	4.4	0.97	46.6	49.7	1.8
45	31	34	1,630	1,905	14.4	84.0	3.6	1.16	50.0	48.9	1.7
46	35	36	1,553	2,060	14.6	86.0	4.1	1.04	43.0	49.7	2.0
47	35	30	1,630	1,950	10.1	60.0	3.7	0.81	34.7	34.0	1.7
48	36	36	1,605	1,830	14.0	83.0	4.0	1.03	50.0	47.6	1.6
49	37	32	1,240	1,465	15.8	92.0	3.9	1.18	46.5	53.7	1.9
50	38	33	1,875	2,130	14.0	82.0	4.1	1.00	47.0	47.6	1.8
51	39	35	1,590	2,480	13.1	78.0	3.6	1.08	39.5	44.8	1.9
52	40	30	1,500	1,750	13.8	80.0	3.8	1.05	53.0	46.9	1.5

50	38	33	1,875	2,130	14.0	82.0	4.1	1.00	47.0	47.6	1.8
51	39	35	1,590	2,480	13.1	78.0	3.6	1.08	39.5	44.8	1.9
52	40	30	1,500	1,750	13.8	80.0	3.8	1.05	53.0	46.9	1.5
53	44	32	1,240	1,570	14.0	82.9	2.9	1.41	50.0	47.6	1.6
54	46	30	1,590	2,050	8.5	50.0	3.6	0.69	34.7	28.9	1.4
55	46	32	1,195	1,395	10.8	63.0	3.4	0.92	34.2	36.7	1.8
56	47	30	1,630	2,095	10.0	59.0	3.4	0.89	35.5	34.0	1.7
57	47	30	1,500 (2 days)	1,835	12.4	74.0	3.7	1.00	46.0	43.5	1.6
58	49	35	1,440	2,120	11.0	65.0	3.1	1.04	47.2	37.4	1.3
59	52	32	1,785	3,065	11.5	68.0	3.5	0.97	31.2	39.0	2.1
60	53	32	1,195 (24 days)	1,505	11.1	66.0	3.3	1.00	31.2	37.7	2.1
61	53	30	1,590	2,315	10.0	59.0	2.9	1.01	29.7	34.0	1.9
62	54	30	1,630	.....	8.5	50.0	3.1	0.80	31.2	28.9	1.6
63	54	30	1,500	1,855	10.8	64.0	3.4	0.94	39.0	36.7	1.5
64	56	32	1,785	3,555	9.0	53.0	3.2	0.82	34.5	30.6	1.5
65	56	35	1,440	2,240	12.3	73.0	3.2	1.14	42.3	41.7	1.7
66	61	30	1,500 (2 days)	2,200	9.2	55.0	3.4	0.80	34.7	31.2	1.6
67	63	31	1,500	2,030	9.0	53.0	3.0	0.88	34.7	30.6	1.5
68	66	32	1,690	2,225	11.3	67.0	3.2	1.04	33.7	38.3	1.9
69	67	32	1,195 (24 days)	1,740	11.0	65.0	2.7	1.20	32.7	37.4	1.9
70	68	30	1,630	2,525	11.1	66.0	3.3	1.00	36.7	37.7	1.8
71	68	30	1,500	2,350	9.0	53.0	2.8	0.94	28.9	30.6	1.8
72	70	35	1,770	3,100	10.6	63.0	2.9	0.78	40.9	35.9	1.5
73	76	35	1,770	3,290	10.8	64.0	2.9	1.10	29.7	36.7	2.1
74	77	30	1,500	2,430	8.5	50.0	2.9	0.86	24.0	28.9	2.0
75	78	32	1,690	2,875	10.6	63.0	2.8	1.12	34.5	35.9	1.7
76	80	34	1,450	2,300	9.8	56.0	3.0	0.93	39.0	33.1	1.4
77	82	30	1,630	2,735	11.0	65.0	3.0	1.08	37.8	37.4	1.7
78	84	31	1,500	2,480	10.2	61.0	3.0	1.01	32.7	34.6	1.8
79	84	32	1,415	2,860	9.2	55.0	3.1	0.88	32.0	31.2	1.7
80	84	36	1,910	2,400	11.0	65.0	2.5	1.30	29.7	37.4	2.1
81	89	32	1,195 (5 days)	2,210	10.2	61.0	3.2	0.95	43.5	34.6	1.4
82	91	33	1,910	.....	11.0	65.1	3.2	1.01	36.7	37.4	1.7
83	98	30	1,630	2,605	9.2	55.0	3.0	0.90	37.7	31.2	1.4
84	98	33	1,680	3,705	11.0	65.0	3.7	0.87	39.5	37.4	1.6
85	98	32	1,415	3,360	9.5	56.0	3.3	0.84	33.7	32.3	1.7
86	99	34	1,825	.....	9.5	56.0	2.9	0.85	29.7	32.3	1.6
87	105	32	1,415	3,570	10.0	60.0	2.9	0.96	31.2	34.0	1.9
88	105	33	1,680	3,705	12.0	71.0	4.3	0.82	36.0	40.8	1.9
89	112	32	1,415	3,550	9.0	53.0	2.9	0.91	27.1	30.6	1.9
90	112	33	1,680	4,085	11.0	65.0	3.8	0.85	41.3	37.4	1.5
91	119	32	1,415	3,655	10.5	62.0	3.2	0.97	30.3	35.7	2.0
92	119	33	1,680	4,150	11.2	67.0	3.5	0.95	35.5	38.0	1.9
93	133	33	1,720	5,491	13.0	77.0	4.3	0.89	13.0	47.2	1.6
94	140	37	1,815	5,505	11.1	67.0	4.2	0.79	43.1	37.7	1.5
95	140	35	1,975	6,125	11.5	68.0	4.3	0.79	35.5	39.0	1.9
96	147	36	2,135	4,820	14.8	86.6	4.3	1.00	48.6	50.1	1.7
97	147	38	2,175	6,380	11.3	67.0	4.3	0.76	36.2	38.3	1.8
98	155	36	2,135	4,810	12.0	70.0	4.3	0.81	42.3	40.8	1.6
99	161	32	1,475	4,175	15.2	90.0	4.9	0.96	44.6	51.6	2.0
100	189	37	2,180	5,080	9.5	56.0	3.6	0.77	31.2	32.3	1.7
101	189	37	2,010	5.695	10.5	63.0	4.0	0.78	36.2	35.7	1.7
102	198	36	1,875	6,805	11.0	65.0	3.6	0.90	32.5	37.4	2.0
103	203	38	2,050	6,710	12.0	75.0	3.8	0.98	45.7	42.7	1.6
104	210	36	1,505	6,960	8.5	50.0	3.7	0.67	30.0	28.9	1.7
105	211	36	1,860	8,135	11.3	67.0	4.3	0.76	31.2	33.8	2.1
106	224	32	1,550	6,080	12.0	71.0	4.1	0.86	36.7	40.8	1.9
107	245	36	2,065	7,900	10.0	59.0	4.5	0.65	29.0	34.0	2.0
108	247	34	1,550	6,350	10.1	60.0	4.5	0.66	32.7	34.0	1.8

* $\frac{\text{Hemoglobin in percentage}}{\text{Whole blood iron in milligrams per hundred cubic centimeters}} = \text{Factor.}$

centimeters of acetone was then added to the contents of each test tube, and the mixtures were shaken well and allowed to cool to room temperature. Then to each tube 5 cc. of three times molar ammonium thiocyanate was added, the contents

TABLE 2.—*Results of Control Determinations of Iron in Blood from the Cord, from Full Term Infants and from Adults*

Case	Source of Blood	Hemoglobin (Newcomer), Gm. per 100 Cc.	Hemoglobin (Newcomer), Percentage	Red Blood Cells, Millions	Color Index	Whole Blood Iron, Mg. per 100 Cc. (Fowweather)	Iron Calculated from Determined Hemoglobin, Mg. per 100 Cc. (Butterfield Factor)	Hemoglobin-Ratio,* Mg. %
1	Cord.....	18.0	106.5	...	....	64.6	61.2	1.6
2	Cord.....	17.1	101.6	...	....	54.3	57.9	1.8
3	Cord.....	15.0	89.0	...	....	54.3	51.0	1.6
4	Cord.....	11.0	65.1	...	....	36.8	37.4	1.7
5	Cord.....	16.1	96.0	...	....	64.1	54.9	1.4
6	Full term infant aged 4 mos.	13.0	77.0	3.9	0.98	40.9	44.0	1.8
7	Full term infant aged 6 mos.	16.0	94.0	4.9	0.95	43.1	54.4	2.1
8	Full term infant aged 5 mos.	10.0	60.0	4.0	0.75	37.7	34.0	1.6
9	Full term infant aged 4 mos.	14.0	83.0	4.7	0.88	41.0	47.1	2.0
10	Full term infant aged 3 mos.	13.0	76.6	4.4	0.87	34.7	44.0	2.1
11	Full term infant aged 3 mos.	14.0	82.0	4.7	0.87	46.2	47.6	1.8
12	Full term infant aged 3½ mos.	10.0	59.0	4.1	0.71	29.7	34.0	2.0
13	Full term infant aged 6½ mos.	10.8	63.0	4.9	0.64	31.0	36.7	2.0
14	I Adult A. M.	18.5	107.0	...	....	59.0	62.9	1.7
15	I Adult A. M.	18.5	107.0	...	....	61.0	62.9	1.7
16	I Adult P. M.	18.5	107.0	...	....	66.6	62.9	1.6
17	I Adult P. M.	17.5	103.0	...	....	62.5	59.5	1.6
18	II Adult A. M.	15.4	91.0	...	....	55.5	52.4	1.6
19	II Adult A. M.	15.4	91.0	...	....	59.0	52.4	1.5
20	II Adult P. M.	16.6	97.0	...	....	66.6	56.4	1.4
21	II Adult P. M.	16.5	96.0	...	....	64.5	56.1	1.4
22	III Adult A. M.	12.5	74.0	...	....	50.0	42.5	1.4
23	III Adult A. M.	13.1	77.0	...	....	48.1	44.5	1.4
24	III Adult P. M.	12.5	74.0	...	....	50.0	42.5	1.7
25	IV Adult A. M.	16.8	98.0	...	....	50.0	57.1	1.5
26	IV Adult A. M.	17.5	103.0	...	....	53.0	59.5	1.9
27	V Adult A. M.	12.5	74.0	...	....	42.0	42.5	1.9
28	V Adult A. M.	12.0	71.0	...	...	44.0	40.8	1.7
29	VI Adult	12.9	75.0	...	....	32.5	42.7	2.2
30	VII Adult	13.5	78.0	...	....	48.0	45.8	1.6
31	VIII Adult	13.5	78.0	...	....	46.2	45.8	1.6

* $\frac{\text{Hemoglobin in percentage}}{\text{Whole blood iron in milligrams per hundred cubic centimeters}} = \text{Factor.}$

were mixed, and water was added to make a total of 50 cc. The unknown and the standard mixture were compared in a colorimeter, the standard being set at 20. From the calculation $\frac{20}{\text{reading}} \times 50$ the number of milligrams of iron per hundred cubic centimeters of blood was determined.

All reagents used in this method must be chemically pure and free from iron. The standard solution of iron was prepared by dissolving 0.7 Gm. of pure ferrous ammonium sulphate in 50 cc. of water. Then 20 cc. of 10 per cent sulphuric acid (iron-free) was added, the mixture was slightly warmed and sufficient tenth-normal solution of potassium permanganate was added to oxidize the ferrous salt completely. When the preparation was diluted to one liter with water, 1 cc. contained 0.1 mg. of iron. The accuracy of this method was checked by performing duplicate determinations on blood from the cord, from full term infants and from adults (table 2). The experimental error was no greater in the series of premature infants than it was in the control group.

Hematologic Methods.—Determinations of the erythrocytes and hemoglobin were made on the premature infants at weekly intervals while they were in the

TABLE 3.—*Results of Determinations of the Whole Blood Iron in Premature Infants*

	Age													
		Weeks							Months					
	New-Born	1	2	3	4	6	8	10	3	4	5	6	7	8
	66.0	60.9	73.5	71.0	46.2	66.6	34.7	34.7	29.7	43.5	47.2	44.6	45.7	36.7
	54.3	65.7	71.4	50.0	54.0	50.0	34.2	34.7	24.0	36.7	43.1	31.2	30.0	29.0
	50.0	68.0	62.5	71.0	55.5	58.9	35.2	33.7	34.5	37.7	35.5	36.2	31.2	32.7
	80.0	54.3	48.0	59.8	54.8	46.6	46.0	32.7	39.0	39.5	48.6	32.5	....	....
	54.3	65.0	56.3	52.0	61.5	50.0	47.2	36.7	37.8	33.7	36.2	....	....	....
	....	49.5	50.0	56.8	54.0	43.0	31.2	28.9	32.7	29.7	42.3	....	....	....
	....	....	55.0	59.5	53.0	34.7	31.2	40.9	32.0	31.2	....	....	....	....
	....	....	55.5	52.6	57.0	50.0	29.7	....	29.7	36.0	....	....	....	....
	....	....	....	57.1	50.0	46.5	31.2	....	....	27.1	....	....	....	....
	....	....	....	57.1	64.5	47.0	39.0	....	....	41.3	....	....	....	....
	....	....	....	....	49.0	39.5	34.5	....	....	30.3	....	....	....	....
	....	....	....	....	....	53.0	42.3	....	....	35.5	....	....	....	....
	....	....	....	....	....	50.0	....	....	....	....	....	....	....	....
Averages	60.7	60.5	59.0	58.7	50.1	48.9	36.4	34.6	32.4	35.2	42.2	36.1	35.6	32.8
Number of determinations	5	6	8	10	11	13	12	7	8	12	6	4	3	3

hospital and at biweekly or monthly intervals after their discharge. United States standard pipets and a Thoma-Levy hemocytometer were used for all erythrocyte counts. A physiologic solution of sodium chloride was used to dilute the erythrocytes. Williams' improved Newcomer hemoglobinometer was used for the determinations of the hemoglobin. The blood was obtained by pricking the heel of the infant, so that a free flow was obtained.

RESULTS

The results of the determinations of iron in the whole blood of the premature infants studied are recorded in table 3. The highest values are for the group of new-born infants, and there is a weekly diminution of the blood iron values, the lowest point being noted at about the twelfth week. The values then rise, and the curve makes a slight peak at the

fifth month and then drops again to a level. The hemoglobin values show a corresponding drop in the early weeks after birth, and the lowest values are noted between the tenth and twelfth week. There is a

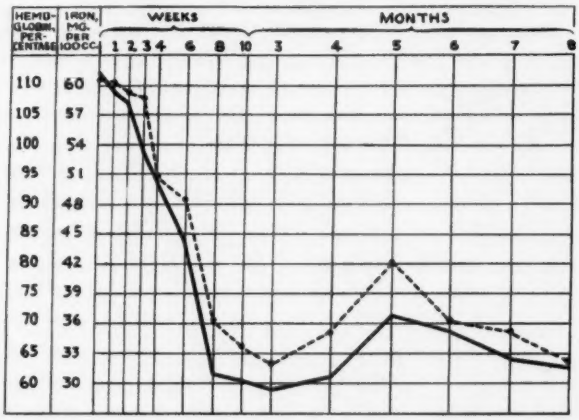

Chart 1.—Curves of the determined values for hemoglobin and blood iron for premature infants during the first eight months of life. The dotted line indicates the milligrams of iron per hundred cubic centimeters; the solid line, the percentage of hemoglobin.

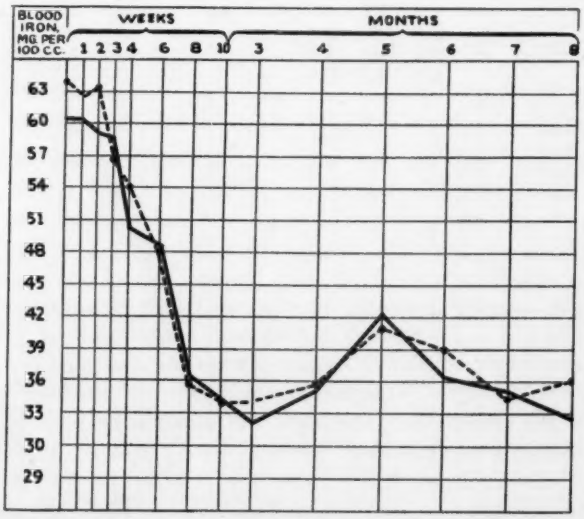

Chart 2.—Curves of blood iron values for premature infants during the first eight months of life. The solid line indicates the blood iron as determined; the dotted line, the iron as calculated from the determined values for hemoglobin.

slight peak in the hemoglobin values at the fifth month, followed by a gradual flattening of the curve to the eighth month (chart 1).

According to the Butterfield factor (iron equals 0.335 per cent of hemoglobin) the amount of iron in the determined number of grams of hemoglobin was calculated in milligrams per hundred cubic centimeters of blood. Thus the amount of iron as actually determined and the amount as estimated from the determined hemoglobin value could be compared (table 4). These values are closely parallel for all the age groups studied (chart 2).

It is of interest to compare the values here reported for whole blood iron and hemoglobin in premature infants with values for full term infants during similar age periods. In making this comparison the figures used for the whole blood iron of full term infants are those of

TABLE 4.—*Average Values for Hemoglobin Percentage, Determined Whole Blood Iron and Iron as Calculated from Determined Grams of Hemoglobin, for Various Age Periods*

Age	Hemoglobin, Percentage (Newcomer)	Iron as Determined, Mg. per 100 Cc.	Iron Calculated from Hemoglobin, Mg. per 100 Cc.
48 hours	112.0	60.7	64.5
1 week	109.0	60.5	62.9
2 weeks	107.5	59.0	64.1
3 weeks	98.9	58.7	56.9
4 weeks	93.5	50.1	53.9
6 weeks	84.0	48.9	48.5
8 weeks	62.0	36.4	35.7
10 weeks	60.2	34.6	34.5
3 months	59.9	32.4	34.4
4 months	61.3	35.2	35.1
5 months	72.5	42.2	41.6
6 months	68.5	36.1	39.2
7 months	64.0	35.6	35.1
8 months	63.3	32.8	36.2

Kotikoff,[2] and the hemoglobin values for full term infants are the means of the values recently reported by several investigators.[8] It is found that the values for the whole blood iron and for the hemoglobin content in both the premature and the full term infants are highest at birth. The rate of fall in the two groups is parallel and the lowest values for both iron and hemoglobin in each group are reached at about the twelfth

8. Mackay, H. M. M.: Factors Causing Variation in the Haemoglobin Level with Age in the First Year of Life, Arch. Dis. Childhood **8**:251 (Aug.) 1933. Kato, Katsuji, and Emery, O. J.: Hemoglobin Content of the Blood in Infancy, Folia haemat. **49**:106, 1933. Elvehjem, C. A.; Peterson, W. H., and Mendenhall, D. R.: Hemoglobin Content of the Blood of Infants, Am. J. Dis. Child. **46**:105 (July) 1933. Merritt, K. K., and Davidson, L. T.: The Blood During the First Year of Life, Am. J. Dis. Child. **46**:990 (Nov.) 1933.

week of life. The curves for the iron and the hemoglobin values are similar in the two groups, the chief difference being that in the

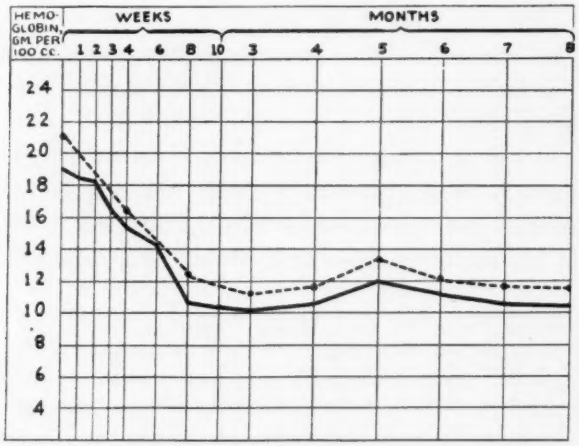

Chart 3.—Curves of hemoglobin values for infants during the first eight months of life. The solid line indicates the values for premature infants; the dotted line, the values for full term infants (a combined curve based on statistics reported recently by various authors).

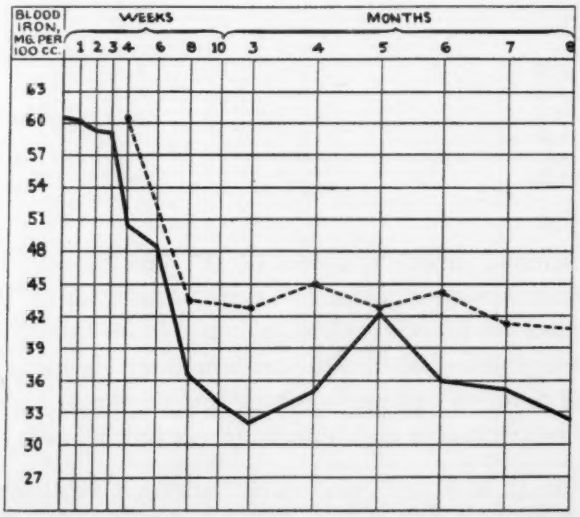

Chart 4.—Curves of blood iron values for infants during the first eight months of life. The solid line indicates the values for premature infants; the dotted line, the values for full term infants (as reported by Kotikoff).

premature infants the hemoglobin and the blood iron reach lower levels at age periods corresponding with those for full term infants (charts 3 and 4).

As previously mentioned, Kotikoff determined a factor

$$\frac{\text{Hemoglobin in Percentage}}{\text{Whole Blood Iron in Milligrams per Hundred Cubic Centimeters}}$$

for the full term infants whom he studied. While he did not make simultaneous determinations of hemoglobin as I have done with the series of premature infants here reported on, his figures are the only ones which are at present available for comparison. I have calculated the hemoglobin-iron ratio of the premature infants here studied and find that the resulting factor rather closely agrees with the factor given by Kotikoff for full term infants at monthly age periods under 1 year (table 5).

TABLE 5.—*Comparison of the Hemoglobin-Iron Ratios for Full Term and Premature Infants* *

Age	Hemoglobin-Iron Ratio, Premature Infants (Abt)	Hemoglobin-Iron Ratio, Full Term Infants (Kotikoff)
New-born	1.82	....
1 month	1.87	1.42
2 months	1.70	1.85
3 months	1.85	1.80
4 months	1.74	1.70
5 months	1.72	1.78
6 months	1.89	1.77
7 months	1.79	1.83
8 months	1.93	1.86
9 months	....	1.96
10 months	....	1.87

* $\frac{\text{Hemoglobin in percentage}}{\text{Whole blood iron in milligrams per hundred cubic centimeters}} = \text{Factor.}$

COMMENT

A study of the relationship of the whole blood iron and the hemoglobin content was undertaken in order to throw some light, if possible, on the mechanism of the anemia of premature infants. From the high values recorded at birth a rapid decline in the amount of hemoglobin occurs, the value reaching the lowest point at about the twelfth week of life. The high values at birth are said to be related to the low intrauterine oxygen tension of the fetus. After birth there are several factors which have a probable bearing on the decline in the hemoglobin values.[9] The increased postnatal oxygen tension causes a decrease in the red blood cells, or hemoglobin carriers; an increased hemolysis of circulating erythrocytes is evidenced in the new-born period by an increased indirect

9. Abt, Arthur F.: The Diagnosis and Treatment of Anemias of Infancy, Illinois M. J. **64**:572 (Dec.) 1933.

van den Bergh reaction and a high icterus index. As a result of the hemolysis of excess red blood cells in the new-born period, the liberated hemoglobin is broken down into bilirubin and iron. Whether the hemoglobin is broken down in the reticulo-endothelial cells or in the circulating blood stream, a great deal of the excess bilirubin is taken out of the circulation by the epithelial cells of the liver and the iron is also removed and stored in the liver, the spleen and other organs.

Two other factors must be considered: Many of the erythrocytes in the blood of the new-born are more immature in development than those formed at a later period. These youthful red blood cells are said to have a diminished osmotic resistance as compared to mature erythrocytes; in other words, they are more fragile and therefore more easily hemolyzed. An extreme example of the occurrence of many immature erythrocytes in the new-born period is the erythroblastosis associated with icterus gravis neonatorum.[10] In this condition the increased hemolysis of the fragile youthful red blood cells is probably a contributory cause of the rapidly developing jaundice and anemia.

In addition to their fragility, the immature erythrocytes are larger than those of later infancy or of adult life. Van Creveld,[11] by measuring the diameter of red blood cells and by using the Price-Jones curves, found that for premature and full term infants the mean diameter was larger directly after birth than at any other time. These larger cells persist in the blood of both full term and premature infants for the first few weeks of life. The size of the red blood cells of the new-born full term infant approximates that of the cells of older infants, in the sixth to the eighth week of life. In the premature infant the diameters of the red blood cells decrease more rapidly than in the full term infant. This variation in the size of the red blood cells is influenced by the oxygen tension, for it is known that a decrease in the oxygen supply leads to an increase in the mean diameter of the erythrocytes while an increase in the oxygen supply decreases the mean diameter.

Another factor to be considered is the difference in the chemical composition of the hemoglobin of the fetus and of the new-born infant from that of the older infant. Bischoff, Schulte and Wundt,[12] in studying the dissociation of hemoglobin with sodium hydroxide, found

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10. Abt, Arthur F.: Erythroblastosis in Icterus Gravis Neonatorum, J. Pediat. **3**:7 (July) 1933.

11. van Creveld, S.: Diameter of Red Blood Cells of Premature Infants and of Those Born at Full Term, Am. J. Dis. Child. **44**:701 (Oct.) 1932.

12. Bischoff, H., and Schulte, H.: Weitere Studien zur Hämoglobinresistenz im Säuglingsalter, Jahrb. f. Kinderh. **112**:56 (March) 1926. Wundt, N.: Beitrag zur Frage der Hämoglobinresistenz, Ztschr. f. Kinderh. **43**:297 (March) 1927.

a greatly increased time interval for the dissociation of hemoglobin in the new-born period. In the blood of premature infants the dissociation time is even longer than in that of full term new-born infants. This more resistant hemoglobin gradually decreases from 80 per cent at the new-born period to 50 per cent at 2 months and to 10 per cent at 4 months; by 1 year it has entirely disappeared from the blood. Haurowitz [13] and more recently Trought [14] demonstrated this difference by the aid of spectroscopic examination. Haurowitz expressed the belief that the difference between the embryonal type of hemoglobin and the hemoglobin found later in life is in the globulin factor of the molecule.

All of these factors—the change in oxygen tension, the increased hemolysis after birth, the fragile, immature red blood cells and the embryonal type of hemoglobin—apply to the premature infant as well as to the full term new-born infant. In addition, the premature infant is born with a smaller total blood volume than the full term infant. The increment of growth is greater in the premature infant, and with the rapid gain in weight and growth there must be a corresponding increase in the blood volume. The demand for the formation of blood in the premature infant is, therefore, probably greater than that in the full term infant because of the more rapid growth. In order that the demand for new blood formation may be adequately fulfilled, the blood-forming mechanism must be capable of rapidly and efficiently responding to the demand for new blood cells, and sufficient and proper materials must be at hand for the manufacturing of the products needed.

Because no way of accurately measuring the efficiency of the formation of blood has been devised, it may be assumed that the somewhat immature blood-forming organs of the premature infant are incapable of fully supplying the new blood needed by the rapidly growing premature infant in the first eight to twelve weeks after birth. This functional incapacity of the hematopoietic system may be compared with the imperfect functioning of the gastro-intestinal, the cardiovascular and the heat-regulating system in the premature infant.

The rapid hemolysis of red blood cells after birth liberates iron, and, as in an internal hemorrhage, the excess of this mineral is not lost from the body but stored chiefly in the liver and spleen; thus a reserve depot for future use is established. With the rapid demand for the formation of new hemoglobin the building stones are probably quickly used up between the third and the sixth month of life. The total amount of

13. Haurowitz, F.: Ueber das Hämoglobin des Menschen, Ztschr. f. physiol. Chem. **186**:141, 1930.

14. Trought, H.: Specificity of Haemoglobins Including Embryonic Haemoglobin, Arch. Dis. Childhood **7**:259 (Oct.) 1932.

blood destroyed in the premature infant must be considerably less than that in the large full term infant, and therefore the amount of iron and other building materials available for the production of new hemoglobin in small premature infants must be considerably less than the supply in larger full term infants.

The premature infant, then, in comparison with the full term infant, has (1) a greater increment of growth and a rapidly increasing blood volume with an accompanying greater demand for the formation of blood, (2) a blood-forming mechanism which is immature and probably functionally incapable of meeting the full demands made on it, and (3) less total blood to start with, probably a smaller amount of blood hemolyzed and, therefore, less iron and building materials stored to meet future demands.

Determinations of Serum Iron.—That all of the iron in the blood is not included in the hemoglobin molecule has been shown by recent studies of the nonhemoglobinous iron of the blood serum. Barkan [15] termed this "the easily split off" or "loosely combined" iron fraction, in contradistinction to the iron in the hemoglobin molecule. Fowell [16] spoke of it as the "free iron of the blood," and Rich [17] termed it "the colorless iron-containing residue of the hemoglobin molecule."

The exact function of the serum iron is unknown. As has been shown, the destruction of blood may occur in the blood stream and in various organs, but the formation of blood occurs chiefly in the red bone marrow. There must, therefore, be an inner circulation of iron, and a considerable amount must be transported in the blood stream. Thoenes [18] recently made an extensive investigation of the iron content of the serum of infants and children in health and disease. The serum iron values for premature infants are similar to the values for full term infants of a corresponding age. External iron metabolism has no definite relationship to the serum iron content. It is uninfluenced by a positive or negative balance of iron. No definite relationship between the hemoglobin level and the serum iron content has been established.

It is probable that the source of the serum iron is a product of the splitting up of the hemoglobin molecule. However, Thoenes was unable to demonstrate an increased serum iron content in new-born infants, in

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15. Barkan, G.: "Leicht abspaltbares" Bluteisen und Blutfarbstoff, Klin. Wchnschr. **11**:1050 (June 18) 1932.

16. Fowell, P. H. C.: Iron in the Blood, Quart. J. Med. **6**:179, 1912-1913.

17. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp. **47**:338 (Dec.) 1930.

18. Thoenes, F., and Aschanffenburg, R.: Der Eisenstoffwechsel des wachsenden Organismus, Abhandlungen aus der Kinderheilkunde und ihren Grenzgebieten, no. 35, Berlin, S. Karger, 1934.

whom increased hemolysis and destruction of hemoglobin are known to occur and an increase in bilirubin is demonstrable. Locke, Main and Rosbash [19] were able to show increased values for serum iron in adults with pernicious anemia, in which condition an increased hemolysis occurs.

Warburg [20] suggested that the serum iron may have the same function as other iron; that is, it may also act as a respiratory ferment. It will require further investigation to determine exactly what rôle the serum iron plays in inner metabolism: whether it is simply a by-product of the destruction of hemoglobin, whether it serves as transport iron, whether it acts also as a respiratory ferment or, finally, whether it has a rôle as a catalyst in aiding or stimulating the formation and regeneration of blood.

Determinations of the serum iron content were not made separately in the series of premature infants for whom data are here presented. In the normal adult the serum contains an average of 0.1 mg. of iron per hundred cubic centimeters, and the amount of iron in the serum of premature infants [18] ranges from 0.058 to 0.19 mg. per hundred cubic centimeters, or an average approximating that of adult blood. As the values for the whole blood iron in the group of premature infants here reported on varied from 60 to 30 mg. per hundred cubic centimeters, a variation of the serum iron value of from 0.05 to 0.2 mg. per hundred cubic centimeters would cause an error of less than 0.1 per cent in the results of the whole blood iron determination, which is well within the experimental error of the method employed.

CONCLUSIONS

1. In the series of premature infants here reported on the values for whole blood iron closely approximated the values for hemoglobin.

2. On comparing the curves for the whole blood iron and the hemoglobin values in the series of premature infants with similar curves for full term infants within the first eight months of life, it was found that the values are equally high at birth and the rates of fall in the two groups are parallel; the lowest values are reached at about the twelfth week of life. The types of the curves are similar, the chief difference being that in premature infants the hemoglobin and the blood iron values reach lower levels at corresponding age periods.

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19. Locke, A.; Main, E. R., and Rosbash, D. O.: Copper and Non-Hemoglobinous Iron Contents of Blood Serum in Disease, J. Clin. Investigation **11**:527 (May) 1932.

20. Warburg, O., and Krebs, H. A.: Ueber locker gebundenes Kupfer und Eisen im Blutserum, Biochem. Ztschr. **190**:143, 1927.

3. The factor

$$\frac{\text{Hemoglobin in Percentage}}{\text{Whole Blood Iron in Milligrams per Hundred Cubic Centimeters}}$$

determined by Kotikoff for full term infants is practically the same as that here reported for premature infants.

4. It has been noted that certain common factors produce the anemia of the full term as well as that of the premature infant during the early months of life. These are the change from a low intra-uterine oxygen tension to the higher postnatal tension of atmospheric air; the increased hemolysis of erythrocytes after birth; the fragility of the immature red blood cells of the new-born, and the embryonal type of hemoglobin, different chemically and spectroscopically from the hemoglobin of older infants.

5. The premature infant differs, in part at least, from the full term infant because he has a relatively more rapid growth, and he should therefore have a more rapidly increasing blood volume with a greater demand for formation of blood; a more immature and probably less efficient hematopoietic system (functional incapacity), and a smaller supply of blood to begin with, which might be expected to yield a more limited amount of blood-building materials. The greater decline in the values for hemoglobin and for whole blood iron in the premature infant as compared with those in the full term infant may be explained by these physiologic factors which are peculiar to prematurity.

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PHOSPHATASE STUDIES ON BIOPSY TISSUE IN PROGRESSIVE MYOSITIS OSSIFICANS

WITH A REPORT OF A CASE

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The evidence supporting Robison's [1] theory of the rôle of phosphatase in the formation of bone is strong in spite of its being largely circumstantial. The observations reported in this case offer further indirect evidence in support of the concept that phosphatase is intimately associated with the process of ossification. We present here a preliminary study of a number of sections of tissue removed for biopsy from a white girl 16 years of age who for nine years had had proved myositis ossificans progressiva and who during this period had been under the observation of one of us (G. K. C.).

REPORT OF CASE

During the course of this study the patient suffered two acute flare-ups of the process, the first in the right biceps muscle and the second in the left pectoralis major muscle. The first biopsy was made on the right biceps muscle about six weeks after the first local signs appeared. At the time the biopsy was made the arm in the region of the biceps muscle showed marked swelling, a reddish-blue color, elevation of the local temperature, woody induration and pain without tenderness. The observations were characteristic of the early stage of each localized lesion of the muscle. About 4 Gm. of the muscle was removed. No evidences of ossification were found at operation or on examination of the roentgenograms and microscopic sections. Within about ten days several other specimens were taken, including old heterotopic bone from the posterior wall of the chest on the left, soft tissue immediately surrounding the bone and cartilage from this site which gave evidence of being in the process of ossification. Normal muscle and a section of rib were also removed through the same incision. Another sample of normal muscle was removed from the right thigh.

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1. Robison, R.: The Possible Significance of Hexose Phosphoric Esters in Ossification, Biochem. J. **17**:286, 1923; The Significance of Phosphoric Esters in Metabolism, New York, New York University Press, 1932; Bone Phosphatase, Ergebn. d. Enzymforsch. **1**:280, 1932.

Five weeks later a lesion was observed in the left pectoralis major muscle, the local signs being essentially the same as those noted in the biceps muscle. When the swelling had reached its height a biopsy was made and a sample of tissue was removed from what seemed to be the center of the lesion. This sample contained skeletal muscle with an abundance of fibrous tissue distributed in such a way that samples of the two types of tissue could be almost completely isolated. It was

Phosphatase Activity, Total Phosphorus and Inorganic Phosphorus of Tissues of a Patient with Proved Myositis Ossificans Progressiva of Nine Years' Duration

Tissue	Description	Source	Phosphatase Activity per 100 Cc. (1:25) Extract, Units*	Phosphorus per 100 Gm., Mg.†	Inorganic Phosphorus per 100 Gm. of Tissue,‡ Mg.
"Diseased" muscle...	Preossification stage	Right biceps	16.4	101 (T)	49.0
Muscle.....	Normal	Right quadriceps femoris	0.02	175 (T)	87.0
Muscle.....	Normal	Latissimus dorsi	0.01	.....	74.0
Heterotopic bone....	Spongy	Posterior wall of chest on left	9.6	.....	18.4
Mixture of soft tissues	.....	From around heterotopic bone	0.43	.....	21.5
Heterotopic cartilage	Contained two very small units of bone	Posterior wall of chest on left	10.5	.....	21.8
Rib.....	Normal	Posterior wall of chest on left	1.7	.....	17.8
Blood plasma.....	.....	.....	0.12§	3.6 (I)	....
Fibrous connective tissue	.....	Left pectoralis major	9.7	.....	84.0
Fibrous connective tissue, some muscle and fat	.....	Left pectoralis major	24.8	.....	61.0
Skeletal muscle.....	.....	Left pectoralis major	3.9	.....	98.0

* The phosphatase activity is expressed as the number of milligrams of inorganic phosphorus liberated per hour from a substrate of sodium-beta-glycerophosphate in glycine—sodium hydroxide buffer at p_H 8.8 at 38 C.

† (T) means total phosphorus and (I) means inorganic phosphorus.

‡ Extracted in seventy-two hours using twenty-five parts of water.

§ This is equivalent to 9 Jenner and Kay [2] units.

hoped that determinations of phosphatase on these two types of tissue would give some indication as to which kind of tissue was primarily involved.

Determinations of phosphatase were made according to the method of Jenner and Kay [2] after a suitable water extract of the tissues had been prepared. The samples of tissue used for determination of the total phosphorus content were

2. Jenner, H. D., and Kay, H. D.: Plasma Phosphatase: III. A Clinical Method for the Determination of Plasma Phosphatase, Brit. J. Exper. Path. **13**:22 (Feb.) 1932.

digested with nitric acid and ashed by the method of Cullen and Wilkins,[3] and the phosphorus was determined colorimetrically by the method of Kuttner and Lichtenstein.[4]

The results of these determinations are given in the table. The sample of biceps muscle in the "preossification" stage showed a phosphatase activity from 800 to 1,600 times that of the normal muscles and several times higher than that of the sample of normal bone. The phosphatase activity of the heterotopic bone was decidedly higher than that of the sample of normal bone.

The sample of tissue from the center of the process in the pectoralis major muscle was such that muscle and fibrous tissue could be separated. The fibrous tissue proved to be much richer in phosphatase than the muscle. In another sample containing principally fibrous tissue there was still higher phosphatase activity.

The inorganic phosphorus content of the plasma was 3.6 mg. per hundred cubic centimeters, which is within the normal range. The serum calcium was 10.7 mg. per hundred cubic centimeters, which is also normal. The phosphatase content of the plasma was normal. A normal value for plasma phosphatase was found in a similar case reported by Burrows.[5]

The total phosphorus concentration of one sample of the diseased muscle was decidedly lower than that of the normal muscle. Although different muscles may normally vary somewhat in the phosphorus content, in this case the content of the diseased muscle was appreciably below the normal range.

The microscopic observations and other studies on this patient will be reported later.

SUMMARY

A number of sections of tissue obtained from a patient with so-called myositis ossificans progressiva were studied for evidence of phosphatase activity. Samples of muscle and fibrous tissue taken from the region of two lesions in the preossification stage proved to have a high phosphatase activity, the fibrous tissue having a much higher activity than the adjacent muscle. The activity in two samples of functionally normal muscle was extremely low. Samples of heterotopic bone and cartilage from an older lesion showed a much higher activity than a piece of normal rib. These observations seem to lend further evidence to the concept that connective tissue is the tissue primarily involved.

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3. Cullen, G. E., and Wilkins, W. E.: Electrolytes in Human Tissue: I. The Digestion of Tissue and Other Biological Material and the Subsequent Determination of Various Electrolytes, J. Biol. Chem. **102**:403 (Oct.) 1933.

4. Kuttner, T., and Lichtenstein, L.: Micro Colorimetric Studies: II. Estimation of Phosphorus: Molybdic Acid-Stannous Chloride Reagent, J. Biol. Chem. **86**:671 (April) 1930.

5. Burrows, H. J.: A Case of Progressive Myositis (Fibrositis) Ossificans, Proc. Roy. Soc. Med. **26**:1330 (Aug.) 1933.

INFECTIOUS MONONUCLEOSIS

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The finding by Paul and Bunnell [1] of an increase of heterophilic antibodies in the blood of patients suffering from infectious mononucleosis is a most important contribution to the knowledge of the disease. Repeated confirmatory reports bear out such a statement (Bunnell,[2] Rosenthal and Wenkebach [3]).

A case is presented to demonstrate the value of an examination of the serum for heterophilic antibodies.

REPORT OF A CASE

History.—A 19 year old white youth was admitted to the Mount Sinai Hospital on Sept. 28, 1933, complaining of pain in the abdomen and the right axilla for five days and of swelling in the right axilla for three days. The pain in the abdomen was at first generalized; it then became localized in the lower portion. The patient had a feeling of distention, but there was no nausea or vomiting. Constipation, lasting three days, was terminated by a cathartic. The past and family histories were unimportant.

Physical Examination.—Enlarged lymph nodes were revealed in the cervical region, in the left axilla and in both inguinal regions. In the right axilla, a mass about the size of a walnut was felt. The nodes were tender, the mass in the right axilla being more so than the others. The spleen was felt about 1 fingerbreadth below the costal margin and was firm and tender. The liver also was enlarged and tender. There was tenderness in the right lower abdominal quadrant. The temperature on the patient's admission was 100.8 F., the pulse rate, 88, and the respiratory rate, 24. Originally acute appendicitis was suspected. The examination of the blood (the details of which will be discussed later) revealed mononucleosis, the mononuclear count being 84 per cent with 14 per cent abnormal lymphocytes. The results of examination of the blood and the clinical picture suggested infectious mononucleosis. The test for heterophilic antibodies established the diagnosis.

A lymph node was removed from the right inguinal region. It was encapsulated, grayish white, soft and spherical, measuring 15 mm. in the largest diameter.

From the Pathological Laboratory of the Mount Sinai Hospital.

Presented before the Chicago Pathological Society, Feb. 12, 1934.

1. Paul, John R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90 (Jan.) 1932.

2. Bunnell, W. W.: A Diagnostic Test for Infectious Mononucleosis, Am. J. M. Sc. **186**:346 (Sept.) 1933.

3. Rosenthal, N., and Wenkebach, G.: Die Bedeutung der heterophilen Antikörperreaktion für die Diagnose der infektiösen Mononucleose, Klin. Wchnschr. **12**:499 (April 1) 1933.

The surface of the section was homogeneous, white and glistening, with a few hemorrhages the size of a pinpoint.

Microscopic Description.—A marked change was seen in the general appearance of the histologic section, as well as in the finer details. The lymph follicles were less distinct; the central, pale area was widened, and the peripheral, dark blue zone was narrowed and broken through by light-colored bridges which connected the pale central parts of the follicles with the extrafollicular portions of the node. The outstanding characteristics were extreme swelling and proliferation of the endothelial cells. They appeared as large, oval or polygonal cells with an indistinct granular cytoplasm. The nuclei were larger than any seen in normal lymph nodes. They were round or oval, sometimes irregular and very pale. Nucleoli were not particularly prominent. The impression gained from the observation of the sections was that of hyperplasia and hypertrophy. The endothelial cells filled all available space. The marginal sinus was broadened and looked like a pale gray ribbon around the node. The swelling of the reticulo-endothelial elements was so excessive that the lymphocytes were few and appeared to be squeezed out of the node. They were present in the form of small groups and chains. The pale central portions of the follicles seemed to consist of such endothelial cells rather than of lymphoblasts. A search of the sections for cells similar to those found in the circulating blood revealed a few cells with dark nuclei rich in chromatin and with purplish-blue cytoplasm. These cells somewhat resembled plasma cells. No other cells were seen which could be considered similar. Nuclear mitoses were abundant; in some high power fields as many as 10 or 12 were counted. The swelling affected also the circulation of the blood, which seemed to be interfered with. The blood vessels were compressed. In some vessels, the lumen appeared almost obliterated by swollen and prominent endothelial cells. Occasional neutrophilic and somewhat more numerous eosinophilic leukocytes were seen. There was no increase of connective tissue or necrosis; a few recent extravasations of blood occurred, but no old hemorrhages. The connective tissue of the capsule was invaded by lymphocytes, which appeared to be squeezed into its lymph spaces.

In summing up the pathologic observations, the examiner was impressed by the predominance of the large, pale, swollen cells. The predominance was due partly to real hyperplasia, as evidenced by an increased multiplication of the cells, and partly to marked swelling of the cells.

Other Laboratory Observations.—Blood smears obtained on September 29 showed that 18 per cent of the cells gave a positive and 82 per cent a negative oxidase reaction. The examination of the urine, the Kolmer complement-fixation test and the Kahn precipitation test for syphilis and the examination of the feces gave negative results. The fragility test of the red blood cells showed beginning hemolysis in a solution of 0.46 per cent sodium chloride and complete hemolysis in a 0.32 per cent solution. The icterus index was 7. The platelet count was 230,000 per cubic millimeter; the reticulocyte count, 0.6 per cent; the bleeding time (Duke's method), two and one-half minutes, and the coagulation time (capillary tube method), three minutes. The blood sugar was 91 mg.; the urea nitrogen, 12 mg., and the uric acid, 5.2 mg., per hundred cubic centimeters of whole blood.

The patient left the hospital on the third day after his admission. He remained under observation. The spleen was not palpable when the patient was again seen on the eighteenth day after the onset of symptoms; the lymph nodes also were not tender, but their size decreased slowly, and some were still distinctly enlarged four and one-half months later.

The red cell count varied from 4,750,000 to 5,380,000. The percentage of hemoglobin (according to the Sahli method) varied from 75 to 99 per cent, and the color index, from 0.8 to 1.0.

The abnormal lymphocytes differed from the normal cells in size and in the appearance of their nuclei and cytoplasm. They were much larger than the normal lymphocytes, and many surpassed in size the large monocytes also. The structure of the nuclei showed deviations in two directions. In some cells the nucleus was finely granular, with vacuoles, and resembled the nucleus of a stem cell. In others, the chromatin structure of the nucleus approximated more or less distinctly that of the nucleus of a plasma cell. The cytoplasm showed uniformly a tendency toward basophilia. The degree and extent of the basophilia varied, but the direction of its progress was always from the periphery toward the center of the cell

TABLE 1.—*Summary of the White Cell and Differential Cell Counts* *

Date, 1933	White Blood Cells	Metamyelocytes, per Cent	Band Forms, per Cent	Segmented Neutrophils, per Cent	Eosinophils, per Cent	Basophils, per Cent	Small Lymphocytes, per Cent	Large Lymphocytes, per Cent	Abnormal Lymphocytes, per Cent	Plasma Cells, per Cent	Monocytes, per Cent	Mononuclear Cells, per Cent
9/29	13,750	..	2 **275**	12 **1,650**	1 **137.5**	1 **137.5**	39 **5,362.5**	24 **3,300**	14 **925**	1 **137.5**	6 **825**	84 **11,550**
9/30	13,300	..	1 **133**	14 **1,862**	..	1 **133**	57 **7,581**	11 **1,463**	13 **1,729**	2 **266**	1 **133**	84 **11,172**
10/10	10,500	..	..	32 **3,360**	1 **105**	2 **210**	33 **3,465**	18 **1,890**	8 **840**	1 **105**	5 **525**	65 **6,825**
10/19	8,900	..	1 **89**	38 **3,382**	3 **267**	1 **89**	48 **4,272**	6 **534**	..	..	3 **267**	57 **5,073**
10/30	7,600	..	..	50 **3,800**	1 **76**	1 **76**	32 **2,432**	14 **1,064**	..	..	2 **152**	48 **3,648**
11/15	9,200	..	..	48 **4,416**	1 **92**	..	30 **2,760**	16 **1,472**	..	..	5 **460**	51 **4,692**
11/29	6,200	2 **124**	..	60 **3,720**	..	..	34 **2,108**	3 **186**	..	1 **62**	..	38 **2,356**
1934 1/20	10,100	..	..	31 **3,131**	1 **101**	1 **101**	55 **5,555**	10 **1,010**	..	..	2 **202**	67 **6,767**
2/ 8	8,600	3 **258**	..	45 **3,870**	1 **86**	..	42 **3,612**	6 **516**	..	..	3 **258**	51 **4,386**

* The differential counts were based on a study of 500 cells. The numbers in bold face type indicate the absolute number of the cells.

or rather toward the nucleus. The peripheral homogeneous and basophilic zone surrounded a pale gray, finely granular, central perinuclear field of the appearance of ground glass. In a few cells, the entire cytoplasm was deeply blue and homogeneous, resembling closely the cytoplasm of a plasma cell. It was interesting to note that there was no apparent relationship between the changes in the nuclei and in the cytoplasm. Occasionally, a cell with a nucleus resembling that of a stem cell had the deep blue cytoplasm of a plasma cell, and, vice versa, a cell with a nucleus resembling that of a plasma cell had cytoplasm with a narrow zone of peripheral basophilia. It is emphasized that while such divergence was noticed it was not frequent.

Another group of cells resembled monocytes in the structure of their nuclei and of the cytoplasm. In some, the differentiation from monocytes was admittedly subjective, which is in agreement with the experience of other writers. The abnormal lymphocytes were last seen eighteen days after the onset of symptoms and were absent when the blood was examined nine days later. The mononucleosis

showed a gradual decline, the number of mononuclear cells reaching the normal level about two months after the onset of the disease. The patient was not seen for almost two months, when he returned for a study of the blood, owing to a slight relapse. A blood smear again showed an increase of the mononuclear cells. His condition improved quickly, and when he was next seen, the mononuclear cells showed a corresponding decrease.

TECHNIC OF AGGLUTINATION OF SHEEP RED CELLS

Paul and Bunnell,[1] Bunnell [2] and Rosenthal and Wenkebach [3] employed the technic which I used in the studies described in my first two reports on heterophilic antibodies in serum disease.[4]

First Method.—The blood serum is inactivated at 55 C. for fifteen minutes. Serum dilutions ranging from 1:4 to 1:1,024 are set up in quantities of 0.5 cc. Five-tenths cubic centimeter of a 2 per cent suspension of washed sheep blood cells is added, and the test tube is filled to 2 cc. with physiologic solution of sodium chloride. The test tube is then shaken and placed in a water bath at 38 C. for one hour and then in an icebox overnight. For reading, the test tube is first inverted three times while its mouth is covered with the finger-tip. When after shaking the sediment of red cells remains unbroken, the result is read as +++; if it breaks up into large particles and the fluid is clear, as ++, and if the particles are fine and the fluid not transparent, as +.

In my opinion, the test for heterophilic antibodies in the diagnosis of infectious mononucleosis may become increasingly important for the differential diagnosis from appendicitis, acute leukemia and diphtheria. The technic just described for agglutination of sheep red blood cells requires incubation overnight in the icebox. That constitutes a serious drawback when speed is indicated, particularly when a surgical procedure may be necessary, for instance, in a case of appendicitis (as in our case), or when specific and quick therapy may be considered, as in a case of diphtheria.

The need for a quick method is met by a technic of agglutination of red cells which I employed in the studies described in my third report on heterophilic antibodies in serum disease.[5]

Second Method.—The serum dilutions range from 1:2.5 to 1:5,120, or higher if necessary. The quantity of the dilution used is 0.25 cc. One-tenth cubic centimeter of a 2 per cent suspension of sheep cells is added. Narrow test tubes, measuring 75 mm. in length and 12 mm. in the external diameter, are used in order to make possible the reading of the results with a microscope. The test tubes are shaken and placed in a water bath at 38 C. for one hour and then in an icebox for one hour. At the end of two hours, the test tubes are shaken until the sediment is suspended, and the results interpreted as +++ and ++ are estimated

4. Davidsohn, I.: Heterophile Antibodies in Serum Sickness, J. Immunol. **16**:259 (March) 1929; Further Studies on Heterophilic Antibodies in Serum Sickness, ibid. **18**:31 (Jan.) 1930.

5. Davidsohn, I.: Heterophilic Antibodies in Serum Disease: Third Report, J. Infect. Dis. **53**:219 (Sept.-Oct.) 1933.

with the naked eye. The result read as + can be fairly accurately estimated with the naked eye, but a finer, more accurate reading is obtained by placing the test tube flat on its side on the stage of the microscope and looking at the cell suspension with the low power of the objective. The titers obtained with the microscope are from one to two dilutions higher than those read with the naked eye.

The advantages of the second technic are the possibility of getting a result in two hours instead of on the next morning and the greater sensitivity of the test. The titer obtained with this method is from five to ten times higher than with the older technic.

TABLE 2.—*Distribution of the Titers of Agglutinins for the Red Cells of the Sheep*

Titer	Controls Not Treated With Horse Serum		Serum-Treated Patients Without Serum Disease		Patients With Serum Disease	
	Number of Cases	Per Cent*	Number of Cases	Per Cent	Number of Cases	Per Cent
<1:2.5 = >0.1 cc....	15	7	..	..	..	..
1:2.5 = 0.1 cc.....	43	20	..	..	..	..
1:5 = 0.05 cc.....	52	24	2	4.5	..	..
1:10 = 0.025 cc.....	66	30	8	18	..	..
1:20 = 0.0125 cc.....	**38**†	18	19	42	3	8
1:40 = 0.0063 cc.....	3	1	8	18	9	24
1:80 = 0.0031 cc.....	..	..	2	4.5	9	24
1:100 = 0.0025 cc....	..	..	4	9	7	19
1:160 = 0.0016 cc....	..	..	1	2	5	14
1:320 = 0.0008 cc....	..	..	1	2	2	5
1:640 = 0.0004 cc....	..	..	..	..	..	..
1:1,280 = 0.0002 cc...	..	..	..	..	..	..
1:2,560 = 0.0001 cc...	..	..	..	..	..	..
1:5,120 = 0.00005 cc..	..	..	..	..	2	5
Total number....	217		45		37	

* The percentage is calculated from the total number (bottom row) of cases in each group.
† The control number in bold face and the dividing lines indicate the borderline titers, which were the highest dilutions in which a sizable number of the control serums showed agglutination.

RESULTS

In view of the presence of agglutinins for sheep red blood cells in the serum of normal persons, it was necessary for the purpose of evaluation to determine the titers in such persons. This I did in connection with a study of a large number of control serums for comparison with the serums of persons inoculated with horse serum and various immune horse serums.

These results are summarized in table 2. It is apparent that the highest titer encountered occasionally among normal persons was 1 : 40 (in only 1 per cent of the cases) ; the remaining 99 per cent had titers of 1 : 20 or less. Sharply contrasted with this is the occurrence of similar low titers in only 8 per cent of patients with serum disease; the remaining 92 per cent had considerably higher titers. Patients who were treated with horse serum but in whom serum disease did not develop showed only a moderate increase of the antisheep cell titers.

In table 3 are presented the average titers of agglutinins for sheep red cells obtained from all the subjects studied. The knowledge of such average titers will be helpful in the evaluation of results obtained in the study of heterophilic antibodies in the blood of patients suspected of suffering from infectious mononucleosis.

It may prove of great value in the future study of the antibodies to establish whether the increase of the antibodies in infectious mononucleosis is specifically heterophilic. For that purpose it will be necessary to establish, as was done in this case, whether nonheterophilic antibodies, for instance, the agglutinins for rabbit cells, are affected and

TABLE 3.—*Average Titers of Agglutinins for Sheep and Rabbit Cells*

Antibody	Controls	Serum-Treated Patients Without Serum Disease	Patients With Serum Disease
Antisheep agglutinin.....	1:6 = 0.0413 cc.*	1:18 = 0.0141 cc.	1:63 = 0.0040 cc.
Antirabbit agglutinin.....	1:83 = 0.0031 cc.	1:143 = 0.0018 cc.	1:167 = 0.0014 cc.

* The numbers expressed in cubic centimeters indicate the smallest amounts of serum necessary for the production of microscopically detectable agglutination.

TABLE 4.—*Level of Heterophilic and Nonheterophilic Antibodies*

Date of Bleeding	Agglutinins For the Red Blood Cells of the Sheep			Hemolysins For the Red Blood Cells of the Sheep				Agglutinins For the Red Blood Cells of the Rabbit		
	+++	++	+	++++*	+++	++	+	+++	++	+
9/29/33	1:80	1:640	1:5,120	1:1,280	1:2,560	1:10,240	1:20,480	..	..	1:40
10/10/33	1:640	1:1,280	1:10,240	..	..	1:640	1:2,560	..	..	1:40
10/19/33	1:40	1:160	1:1,280	1:40	1:80	1:160	1:640	..	..	..
10/24/33	1:40	1:320	1:1,280	..	1:40	1:320	1:2,560	..	1:10	1:80
11/ 4/33	1:5	1:320	1:1,280	..	..	1:320	1:1,280	..	1:10	1:80
11/10/33	1:40	1:320	1:640	..	1:40	1:320	1:640	..	1:10	1:80
11/15/33	1:10	1:80	1:160	..	1:10	1:40	1:160	1:2.5	1:10	1:80
11/29/33	..	1:20	1:80	..	..	1:20	1:80	1:2.5	1:10	1:80
1/20/34	..	1:5	1:20	..	..	..	1:5	1:2.5	1:10	1:80
2/ 8/34	..	..	1:20	..	..	..	1:20	1:5	1:10	1:80

* + indicates a trace of hemolysis; ++ and +++ indicate the two next higher degrees of hemolysis; ++++ indicates complete hemolysis.

to what extent. For that purpose, the average titers of agglutinins for rabbit cells in normal persons and in those treated with horse serum are appended in table 3. More detailed data concerning the titers of antibodies for rabbit red cells will be found in a previous publication.[5]

In table 4 the titers of agglutinins and of hemolysins for sheep red cells are summarized. The agglutinins for the red cells of rabbits were studied in order to establish the specific heterophilic nature of the increase of the antibodies. For the titration of the hemolysins, the same technic was employed as for that of agglutinins, but 0.25 cc. of a 10 per cent solution of guinea-pig complement was added prior to the addition of 0.25 cc. of the suspension of sheep cells. The titer of the agglutinins for the red cells of the sheep was found to equal, on the sixth day of illness, the highest titer ever encountered during serum

disease. Only 5 per cent of the patients with serum disease had such a high titer. In a large majority (95 per cent) of patients with serum disease the titer did not rise above 1 : 320. On the seventeenth day of illness the titer was still higher; it was lower on the twenty-sixth day and remained at the lower level for about three more weeks. Afterward, the drop was more precipitous. Two months after the onset of illness, the titer was still above the highest normal value. It was found to be normal two months later.

There is a general parallelism between the titers of agglutinins and those of hemolysins for sheep red cells, but I have noticed repeatedly interference with hemolysis in the presence of a high titer of agglutinins. The interference becomes more apparent when the titers for complete hemolysis (+ + + +) are evaluated with those for a trace of hemolysis (+). Such titers in normal persons and in serum-treated control subjects were analyzed in a previous report,[5] to which the reader is referred for details.

The serum of only 2 per cent of normal persons hemolyzed completely the red blood cells of the sheep in a higher dilution than 1 : 40, while 49 per cent of those with serum disease had such a high titer. The comparative evaluation of traces of hemolysis (+) shows a similar behavior with due consideration to the differences in titer. Only 1.5 per cent of the normal controls showed a trace of hemolysis of the red cells of the sheep in dilutions higher than 1 : 320, but the serum of 49 per cent of those with serum disease hemolyzed blood cells in such high dilutions.

The behavior of hemolysins for sheep cells in my case of infectious mononucleosis was rather unusual, because complete hemolysis occurred on only two occasions and only at the first examination was the titer high. At the second examination it was within normal limits. On the other hand, the titer of the lowest degree of hemolysis was extremely high for about seven weeks. Judging by the high titers of agglutinins, complete hemolysis would be expected to occur in considerably higher dilutions than is apparent in the table. Two possible explanations suggest themselves: (1) The marked clumping of the red cells by the serum interferes with lysis by the complement, or (2) the complement of the guinea-pig serum, which is known to contain heterophilic antigen, combines with the heterophilic antibody of the human serum and is not available for the process of lysis. This phase of the problem is being investigated further. The inhibition of complete hemolysis is of practical importance because it may throw light on the reports in the literature of false positive reactions to the Wassermann test which were observed in cases of infectious mononucleosis.

From the comparative study of the hemolysins and agglutinins for sheep red cells that I have described, it is apparent that for more than

one reason the agglutinin titer is preferable to the hemolysin titer as an indicator of the level of heterophilic antibodies.

The agglutinins for the red cells of the rabbit were within the normal limits and remained constant during the entire period of observation. That finding meets the possible objection that the increase in the antibodies is of a nonspecific, nonheterophilic nature.

TOXICITY OF THE SERUM FOR THE GUINEA-PIG

Serums containing heterophilic antibodies are known to be highly toxic for the guinea-pig.[6] A guinea-pig weighing about 360 Gm. was given injections in the jugular vein of 0.4 cc. of serum which was obtained on the seventh day of illness. The serum was kept in the icebox for fifteen days before it was injected. A marked weakness of the right half of the body with temporary paralysis of the right hindleg developed. This was followed by clonic convulsions, labored breathing and sneezing. The maximum reaction was reached in about ten minutes, but some reaction was still distinct at the end of one hour. The high degree of toxicity of the serum corroborates the assumption that the increase of the antibodies is heterophilic in character.

SUMMARY

What is the value of the test for heterophilic antibodies? The finding of an elevated titer of agglutinins for sheep red cells in a person who has not recently received an injection of horse serum or immune horse serum and who presents a clinical picture and the hematologic findings suggestive of infectious mononucleosis indicates with a high degree of probability the presence of infectious mononucleosis.

How high must that titer be to permit such a conclusion? If a fairly reliable history can be obtained indicating the absence of the injection of any form of horse serum in the recent past, a titer of at least 1:64 with the first method and of 1:160 with the second may be considered as positive evidence. A titer of over 1:64 with the first method and of over 1:160 with the second method should be considered as a positive reaction, even if there is a history of administration of horse serum, unless the patient is suffering at the time of examination, or has recently suffered, from serum disease. Such titers were encountered mainly in the course of serum disease and for relatively short periods afterward. Fortunately, most of the reported titers in cases of infectious mononucleosis were considerably higher than those found after administration of horse serum.

6. Ramsdell, Susan G., and Davidsohn, I.: The Toxicity of Human Serum for the Guinea Pig, J. Exper. Med. **49**:497 (March) 1929.

The test offers also a reliable means of a specific diagnosis which was not available heretofore. When applied on a large scale, it will permit a classification of many unsolved problems connected with infectious mononucleosis, for instance, the relation of epidemic to sporadic cases and of the so-called monocytic and lymphocytic anginas to each other and to true infectious mononucleosis. The test will have a great differential diagnostic value, particularly for the exclusion of early cases of acute leukemia. It may be claimed that it is superfluous to have a special serologic test for the separation of infectious mononucleosis from acute leukemia. However, there is evidence in the literature that such errors in differentiation have been made, and not only by beginners. No less an authority than the old master of hematology Tuerk diagnosed his first case of infectious mononucleosis as one of acute lymphadenosis, and only the further course of the disease proved that he had made a mistake.

There are cases of infectious mononucleosis with abdominal symptoms which resemble closely an attack of acute appendicitis. Every experienced surgeon recalls cases with acute abdominal symptoms in which an operation revealed an appendix without gross or histologic evidences of inflammatory changes but with lymphatic hyperplasia and the presence of markedly swollen mesenteric lymph nodes. There is no way of knowing how many of those cases have been instances of infectious mononucleosis with abdominal symptoms. The case which occasioned this study was of such nature. As happened in this case, the test may eliminate the need for operative intervention if such a possibility is kept in mind. It seems probable from certain reports in the literature that cases of infectious mononucleosis with severe anginal lesions are mistaken for cases of diphtheria and the patients are treated for that disease. In all these cases, and probably in other types, the diagnosis of infectious mononucleosis by means of a positive serologic test will enable one to eliminate unnecessary therapeutic procedures and make an absolutely favorable prognosis.

What conclusions may be drawn from the serologic findings as to the nature of the etiologic agent of infectious mononucleosis? In view of the fact that serum disease is at present the only other clinical entity with similar serologic findings, conclusions based on the analogy seem permissible. It is a well established fact that the rise of heterophilic antibodies in serum disease is due to the presence of heterophilic antigen in horse serum.[7] From such analogy there appears sufficient justification for the assumption that, similarly, the serologic changes in the blood of patients with infectious mononucleosis are due to the

7. Davidsohn, I., and Ramsdell, Susan G.: Horse Serum as a Heterophilic Antigen, J. Immunol. **17**:365 (Oct.) 1929. Davidsohn, footnotes 4 and 5.

presence of heterophilic antigen in the virus which is responsible for the disease. From the high titer of the antibodies which has been found in most cases of patients with infectious mononucleosis, it would seem that the virus contains large quantities of heterophilic antigen, and from the fact that the high titer of antibodies was observed to persist for long periods of time, it would further seem that the virus remains in the body for a considerable time after the subsidence of clinical symptoms. On the other hand, heterophilic antigen is known to be present in certain bacteria, for instance, in members of the paratyphoid and of the dysentery group. No reports are available of observations of an increase of heterophilic antibodies in the serum of patients afflicted with diseases caused by one of these micro-organisms. I studied serums from a few patients suffering from infections with paratyphoid bacilli without finding an increase of heterophilic antibodies. The lack of such a rise may be explained by the experimental evidence that the amount of heterophilic antigen in all the aforementioned bacteria is relatively low.

CONCLUSIONS

A case of infectious mononucleosis is presented to illustrate the diagnostic value of the test for heterophilic antibodies.

A technic of agglutination is suggested which is preferable to the older method because it permits the reading of results at the end of two hours and is more sensitive.

GROWTH AND BASAL METABOLISM

IV. CHANGES IN THE BASAL METABOLISM OF CHILDREN DURING A YEAR

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In studying the growth of children there are two types of experimental methods: mass observation of a large number of children at various ages and individual observation of a few children throughout a year or more. Each of these methods has distinct merits and both of them should be employed.

In previous studies of the growth of children, these two experimental methods have been applied only to the increase in weight and height, not to the basal metabolism. The reason that the basal metabolism of children has not been investigated is that most children, on account of their whimsical nature, can hardly bear patiently an experiment which lasts for a long time and which must be repeated several times during a year. The success of the experiments, therefore, depends on the availability of suitable children. For this experiment I chose twenty-six children from a large group on whom I had previously made mass observations.

EXPERIMENTAL METHOD

This report covers a study of the basal metabolism, together with weight and height, of twenty-six children, aged from 3 years and 10 months to 11 years and 2 months, every other month throughout a year (table 1). As the experimental method that was used has been described in detail in a previous paper,[1] only a brief summary is given here:

Previous Diet.—A diet rich in protein seems to increase the basal metabolic rate, and a diet rich in carbohydrate, according to Krogh, results in the lowest figures. To minimize such influences and to have the conditions of the experiments alike as far as possible, the children all had dinner at the institute the night before the experiments were conducted (table 2).

Alcohol Checks.—For measuring the production of heat a Benedict respiration apparatus with cot chamber was used. The accuracy of the calorimeter was tested by burning alcohol in the apparatus at frequent intervals during the course of the

From the Imperial Government Institute for Nutrition, Koisikawa-ku, Tokyo, Japan.

1. Nakagawa, I.: Growth and Basal Metabolism: I. Basal Metabolism of Preschool Children, Am. J. Dis. Child. **47**:963 (May) 1934.

year. In this manner the amount of carbon dioxide produced and the amount of oxygen consumed were exactly calculated and it was found that the respiratory quotient obtained compared satisfactorily with the theoretical figure 0.666.

Calculation of Results.—The production of heat was calculated from the amount of carbon dioxide produced, the oxygen consumed and the nitrogen excreted in

TABLE 1.—*Age of the Children at the Beginning of the Experiment and the Number of Experiments Performed*

Boys					Girls				
		Age		Number of Experiments			Age		Number of Experiments
Child No.	Name	Yrs.	Mos.		Child No.	Name	Yrs.	Mos.	
1	S. N.	3	10	7	1	S. N.	4	0	3
2	N. M.	5	2	4	2	T. I.	4	10	6
3	M. S.	6	6	7	3	M. O.	5	9	4
4	K. M.	6	11	7	4	T. K.	6	1	6
5	Ma. S.	7	0	7	5	T. W.	6	10	7
6	T. S.	8	4	7	6	S. M.	8	1	7
7	Y. I.	8	9	6	7	T. T.	8	4	7
8	To. S.	9	7	7	8	Te. K.	8	6	7
9	H. N.	10	2	4	9	S. K.	8	10	7
10	I. S.	10	9	7	10	H. H.	8	11	7
11	K. K.	10	11	4	11	F. M.	9	11	7
					12	Se. N.	10	1	7
					13	M. S.	10	3	7
					14	K. T.	10	11	7
					15	S. S.	11	2	6
Total				67	Total				95

TABLE 2.—*The Diet Received Previous to the Experiment*

Boys and Girls, Aged from 5 to 7				Girls, Aged from 8 to 10			
Food	Amount, Gm.	Protein, Gm.	Total Caloric Intake	Food	Amount, Gm.	Protein, Gm.	Total Caloric Intake
Fowl	45	8.8	68	Fowl	65	12.7	99
Egg	50	6.6	83	Egg	50	6.6	83
Banana	60	0.8	35	Banana	60	0.8	35
Radish	10	0.1	1	Radish	10	0.1	1
Butter	2	...	19	Butter	3	...	28
Rice	77	5.6	271	Rice	92	6.6	323
Total		21.9	477	Total		26.8	569
Boys, Aged from 8 to 10				**Boys and Girls, Aged from 11 to 14**			
Fowl	80	15.6	122	Fowl	85	17.8	139
Egg	50	6.6	83	Egg	60	7.5	95
Banana	60	0.8	35	Banana	60	0.8	35
Radish	10	0.1	1	Radish	10	0.1	1
Butter	3	...	28	Butter	3	...	28
Rice	108	7.8	377	Rice	123	8.9	431
Total		30.9	646	Total		35.1	729

the urine. The amount of oxygen was multiplied by the caloric value of 1 liter of oxygen at the observed nonprotein respiratory quotient. (This value was obtained from the Zuntz-Schumburg table.[2]) Urine was collected before and after each experiment.

2. Zuntz, N., and Schumburg, W.: Studien zu einer Physiologie des Marsches, Berlin, A. Hirschwald, 1901.

EXPERIMENTAL RESULTS

A summary of the findings is given in table 3.

TABLE 3.—*Experimental Results*

Date of Experiment	Weight, Kg.	Height, Cm.	Oxygen Consumed	Respiration Quotient	Urine Nitrogen Excreted	Calories Per Hour	Calories Per Kg. per Day
BOYS							
S. N. (Born, Jan. 10, 1929)							
11/ 7	13.45	94.8	7.25	0.79	0.238	34.1	60.8
12/19	14.20	95.9	7.03	0.89	0.193	34.0	57.5
2/27	14.15	97.0	8.19	0.92	0.267	39.7	67.3
5/ 9	14.05	98.3	7.14	0.91	0.236	34.6	59.0
7/11	14.05	99.5	7.61	0.81	0.142	36.2	61.9
9/13	14.35	100.8	6.82	0.88	0.217	32.8	54.9
11/21	14.70	101.5	7.13	0.98	0.327	34.8	56.9
N. M. (Born, Aug. 15, 1927)							
10/ 2	14.90	99.2	7.26	0.83	0.223	34.5	55.5
12/12	15.10	100.9	7.62	0.83	0.229	36.3	57.7
3/ 7	15.35	102.2	7.31	0.90	0.203	35.4	55.4
11/12	16.60	106.2	7.80	0.85	0.325	37.0	53.5
M. S. (Born, March 12, 1926)							
9/16	19.55	113.1	9.02	0.85	0.276	43.1	52.9
11/14	20.55	113.2	8.38	1.04	0.278	43.6	51.0
1/16	21.05	113.9	10.07	0.87	0.298	48.4	55.2
3/20	21.40	114.0	8.35	1.04	0.309	41.4	46.4
5/16	22.00	116.4	8.89	1.01	0.320	43.9	47.9
7/18	21.95	117.7	8.19	0.95	0.305	39.9	43.7
9/18	22.20	118.3	9.10	0.88	0.242	43.9	47.5
K. M. (Born, Dec. 6, 1925)							
10/24	19.55	118.1	7.77	0.84	0.405	36.6	44.9
12/30	20.10	118.8	8.11	0.97	0.352	39.6	47.3
3/12	20.05	120.0	7.68	0.98	0.363	37.4	44.8
5/ 7	20.10	120.8	7.59	0.90	0.350	36.3	43.4
7/ 4	20.20	122.5	7.59	0.96	0.446	36.6	43.5
9/ 3	20.35	122.9	8.13	0.89	0.297	39.1	46.1
11/ 1	20.60	124.3	8.11	1.02	0.361	39.8	46.4
Ma. S. (Born, Sept. 14, 1925)							
9/17	17.35	110.4	7.69	0.90	0.257	37.2	51.4
11/15	18.40	111.3	8.34	0.98	0.286	41.0	53.5
1/17	18.20	112.2	9.00	0.89	0.272	43.5	57.3
3/14	18.65	112.5	8.00	1.00	0.322	39.3	50.6
5/15	19.30	114.3	7.85	0.89	0.299	37.7	46.9
9/ 3	19.30	114.8	7.27	1.00	0.273	35.8	44.5
9/23	20.05	114.8	7.65	0.97	0.257	37.6	45.0
T. S. (Born, June 29, 1924)							
10/30	21.55	122.9	8.84	0.89	0.300	42.3	47.1
12/27	22.45	123.0	10.52	9.82	0.277	50.0	53.5
2/26	22.40	124.0	8.94	0.88	0.248	43.1	46.1
4/23	22.70	124.2	9.44	0.86	0.313	45.1	47.7
6/25	23.25	125.4	9.14	0.86	0.303	43.8	45.2
8/27	22.95	127.4	8.78	0.92	0.317	42.5	44.5
11/ 5	24.75	127.8	10.06	0.92	0.398	48.7	47.2
Y. I. (Born, Feb. 16, 1924)							
11/29	20.35	115.4	8.79	0.88	0.263	42.4	50.0
3/12*	19.60	116.1	8.54	0.88	0.277	41.0	50.2
5/14	20.75	116.9	8.57	0.87	0.271	41.1	47.6
7/10	20.90	118.1	9.06	0.85	0.291	43.2	49.6
9/11	21.20	118.9	8.08	0.97	0.320	39.5	44.7
11/20	22.15	119.2	8.90	0.96	0.360	43.4	47.0
To. S. (Born, Feb. 5, 1923)							
9/ 4	23.90	128.3	9.37	0.91	0.392	45.2	45.4
11/ 1	23.85	129.2	9.06	0.86	0.349	43.1	43.4
1/ 7	25.40	130.2	9.80	0.95	0.293	48.0	45.3
3/ 6	25.00	130.3	9.17	0.98	0.405	44.8	43.0
5/ 7	25.10	130.3	9.55	0.84	0.365	45.3	43.3
7/ 3	26.30	132.5	9.48	0.98	0.464	46.2	42.2
9/ 4	25.45	133.4	9.71	0.88	0.386	46.5	43.9
H. N. (Born, Aug. 26, 1922)							
11/ 6	21.05	118.4	7.63	0.92	0.364	36.7	41.9
1/ 8	22.00	119.0	8.17	0.98	0.329	40.0	43.6
3/30	22.90	120.6	8.08	1.01	0.430	39.4	41.3
6/18	22.25	121.4	7.46	0.97	0.352	36.3	39.1

* This child had been ill with a cold for three weeks but he had recovered two weeks before the experiment was performed.

TABLE 3.—*Experimental Results—Continued*

Date of Experiment	Weight, Kg.	Height, Cm.	Oxygen Consumed	Respiration Quotient	Urine Nitrogen Excreted	Calories	
						Per Hour	Per Kg. per Day
I. S. (Born, July 31, 1921)							
5/15	30.70	141.8	11.43	0.83	0.203	54.7	42.8
7/10	30.50	143.2	9.84	1.01	0.365	48.5	38.2
9/11	31.05	144.0	11.02	0.83	0.263	52.6	40.7
11/21	31.85	144.6	11.34	0.86	0.370	54.2	40.8
1/15	33.15	145.5	11.77	0.87	0.465	56.2	40.7
4/ 3†	33.35	146.8	11.36	1.04	0.334	56.6	40.7
6/ 4	33.95	148.4	11.45	0.89	0.348	55.4	39.2
K. K. (Born, Dec. 17, 1921)							
11/ 6	26.35	136.1	9.22	0.91	0.327	44.6	40.8
1/ 8	27.85	137.4	11.32	0.83	0.427	53.6	46.2
3/30	28.75	138.8	10.74	0.92	0.620	51.4	42.9
6/18	28.40	139.4	9.95	0.83	0.390	47.1	39.8
S. N. (Born, Nov. 5, 1928)							
11/ 8	15.00	98.1	7.00	0.80	0.203	33.0	52.8
3/ 5	15.05	100.8	6.37	0.94	0.209	31.2	49.7
9/10	15.90	104.4	6.58	0.93	0.981	32.3	48.8
T. I. (Born, Feb. 9, 1928)							
11/29	14.45	96.7	6.25	0.98	0.227	30.7	51.0
3/ 6	13.95	97.5	6.51	0.89	0.189	31.4	54.1
5/14	13.80	97.8	6.27	0.96	0.205	30.8	53.5
7/10	14.90	99.7	6.67	0.87	0.207	32.0	51.5
9/11	15.55	100.3	7.23	0.83	0.222	34.4	53.1
11/20	15.95	101.3	6.68	0.87	0.185	32.2	48.4
M. O. (Born, Feb. 4, 1927)							
10/24	19.35	108.8	7.91	0.78	0.251	37.0	45.9
1/31	19.95	110.7	9.01	0.83	0.228	42.9	51.6
5/14	20.50	111.4	7.73	0.99	0.258	38.1	44.6
8/ 3	20.95	113.9	7.35	0.99	0.360	35.9	41.1
T. K. (Born, Oct. 13, 1926)							
11/ 7	19.85	115.6	7.93	0.82	0.249	37.5	45.4
1/23	20.15	116.7	9.12	0.83	0.283	43.4	51.6
5/21	21.20	118.8	7.32	0.96	0.249	35.8	40.5
7/16	21.35	120.6	7.33	0.97	0.294	35.8	40.3
9/17	21.75	121.0	8.26	0.85	0.265	39.4	43.5
11/19	22.50	122.9	7.70	0.98	0.305	37.8	40.3
T. W. (Born, Nov. 25, 1925)							
10/ 9	17.45	114.2	7.61	0.87	0.211	36.6	50.3
12/11	18.20	114.8	7.88	0.90	0.251	38.1	50.2
2/19	18.20	116.1	7.72	0.94	0.229	37.8	49.8
4/16	18.55	116.5	8.22	0.91	0.265	39.8	51.6
6/19	18.65	117.9	7.52	0.92	0.275	36.4	46.9
9/ 8	18.30	119.4	7.76	0.91	0.312	37.4	49.1
10/10	19.00	119.6	7.67	0.94	0.276	37.4	47.2
S. M. (Born, Sept. 12, 1924)							
10/ 5	20.40	123.2	7.37	0.91	0.302	35.5	41.8
12/ 5	21.70	124.2	8.06	0.88	0.374	38.5	42.5
1/30	22.25	124.8	8.90	0.90	0.427	42.6	46.0
4/ 2	22.65	125.7	7.43	0.96	0.347	36.1	38.3
6/ 8	22.50	127.3	7.02	1.01	0.385	34.2	36.5
9/10	22.55	128.4	7.41	0.97	0.354	36.1	38.4
10/ 3	23.00	129.3	7.47	0.93	0.308	36.2	37.8
T. T. (Born, July 25, 1924)							
11/23	21.00	120.5	8.18	0.84	0.209	39.1	44.7
1/22	21.40	121.4	8.92	0.88	0.286	42.9	48.1
3/19	21.40	122.5	8.56	0.84	0.205	41.0	46.0
5/21	22.20	122.6	8.12	0.85	0.211	38.9	42.1
7/16	22.20	124.2	8.13	0.86	0.282	38.7	41.8
9/17	22.20	125.3	7.84	0.86	0.225	37.6	40.6
11/23	23.40	125.3	8.78	0.86	0.242	42.1	43.2
Te. K. (Born Jan. 1, 1924)							
7/14	22.40	121.8	8.36	0.89	0.251	40.3	43.1
9/10	22.45	122.7	8.83	0.84	0.247	42.1	54.0
11/ 8	24.05	123.7	8.26	0.99	0.268	40.7	40.7
12/31	23.90	123.7	9.25	0.83	0.281	43.9	44.1
3/ 5	24.70	125.1	8.48	0.93	0.324	41.2	40.0
5/ 7	24.90	126.2	8.05	0.94	0.327	39.1	37.7
7/ 2	24.40	127.6	8.53	0.89	0.241	41.2	40.6
S. K. (Born, Jan. 16, 1924)							
11/23	25.85	130.5	8.99	0.90	0.404	43.1	40.1
1/22	27.10	131.2	9.38	0.89	0.369	45.1	39.9
3/19	28.25	132.2	9.02	0.93	0.346	43.8	37.2
5/21	28.10	133.5	8.75	0.90	0.259	42.4	36.2
7/16	27.40	135.0	8.25	0.91	0.312	39.8	34.9
9/17	27.80	135.2	8.38	0.93	0.212	41.0	35.4
11/19	28.20	135.6	8.94	0.97	0.250	44.0	37.5
H. H. (Born, Jan. 2, 1924)							
11/22	22.80	125.8	8.41	0.95	0.394	40.8	43.0
2/ 5	24.05	126.8	9.46	0.88	0.386	45.3	45.2
4/ 9	24.35	127.9	8.62	0.91	0.382	41.4	40.8
6/25	24.90	129.3	8.67	0.94	0.384	42.0	40.5
8/29	25.15	130.2	8.35	0.95	0.358	40.6	38.8
10/ 1	25.10	130.4	8.59	0.95	0.313	41.9	40.1
11/23	25.95	131.5	8.43	0.96	0.290	41.3	38.2

† This child had had a severe cold two weeks before the experiment was performed.

TABLE 3.—*Experimental Results—Continued*

Date of Experiment	Weight, Kg.	Height, Cm.	Oxygen Consumed	Respiration Quotient	Urine Nitrogen Excreted	Calories	
						Per Hour	Per Kg. per Day
F. M. (Born, Dec. 6, 1922)							
10/23	24.00	129.7	8.20	0.84	0.360	38.8	38.8
12/31	25.00	130.9	8.93	0.83	0.402	42.1	40.4
3/ 5	25.55	131.2	8.11	0.89	0.378	38.8	36.4
5/ 2	26.05	131.7	8.42	0.87	0.434	39.9	36.7
7/ 9	25.80	134.3	8.21	0.88	0.396	39.1	36.4
9/ 9	27.05	135.6	8.47	0.85	0.448	39.9	35.4
10/23	27.75	136.6	8.20	0.92	0.459	39.3	34.0
Se. N. (Born, May 5, 1922)							
5/22	25.00	135.4	9.26	0.85	0.329	44.1	42.3
7/17	24.90	137.4	8.66	0.89	0.289	41.7	40.2
9/23	25.65	138.7	9.64	0.83	0.345	45.7	42.7
11/27	26.75	139.9	9.41	0.89	0.351	45.2	40.5
1/29	28.60	141.3	10.42	0.87	0.342	50.0	41.9
4/ 2	29.30	143.3	9.87	0.90	0.376	47.5	38.9
6/20	30.60	145.5	9.53	0.89	0.457	45.5	35.7
M. S. (Born, July 30, 1922)							
10/30	32.35	140.0	9.14	0.95	0.416	44.4	32.9
12/27	32.75	140.8	9.34	0.93	0.375	45.3	32.2
2/26	34.00	141.8	9.49	0.90	0.394	45.7	32.3
4/23	33.80	142.7	9.39	0.89	0.337	45.2	32.1
6/25	34.75	144.3	9.48	0.97	0.316	46.6	32.2
8/27	34.30	145.9	9.25	1.06	0.294	46.2	32.3
11/ 5	35.70	146.1	10.15	0.85	0.338	48.4	32.5
K. T. (Born, Dec. 25, 1921)							
12/ 4	23.00	127.3	7.84	0.93	0.361	37.9	39.5
2/ 5	23.75	128.5	8.40	0.92	0.261	40.8	41.2
4/16	24.65	129.8	8.35	0.90	0.368	40.1	39.1
6/27	25.70	132.1	8.98	0.83	0.252	42.8	40.0
9/10	27.45	133.8	8.86	0.93	0.252	43.2	37.7
10/22	27.95	135.0	9.02	0.92	0.329	43.7	37.5
12/ 3	28.15	135.9	8.99	0.92	0.246	43.9	37.4
S. S. (Born, March 3, 1921)							
5/15	29.80	136.9	9.76	0.82	0.274	46.4	37.4
7/10	28.85	138.2	9.42	0.86	0.228	45.3	37.7
9/11	30.35	139.6	10.49	0.78	0.265	49.4	39.1
11/21	31.55	141.1	9.71	0.88	0.290	46.7	35.5
1/15	32.60	141.4	10.77	0.80	0.329	50.7	37.3
4/ 3	34.35	142.8	10.41	0.84	0.325	49.6	34.7

The annual increase in the total production of heat and the increase in weight and height are shown in table 4. The increase in the produc-

TABLE 4.—*Yearly Increase in Weight, Height and Total Production of Heat*

Boys		Age*		Experimental Period		Weight, Kg.	Height, Cm.	Calories per Day
No.	Name	Yrs.	Mos.	Start, 1932	End, 1933			
1	S. N.	3	10	11/ 7	11/21	1.25	6.7	18
3	M. S.	6	6	9/16	9/18	2.65	5.2	20
4	K. M.	6	11	10/24	11/ 1	1.05	6.2	78
5	Ma. S.	7	0	9/17	9/23	1.95	4.4	66
6	T. S.	8	4	10/30	11/ 5	3.20	4.9	153
7	Y. I.	8	9	11/29	11/20	1.80	3.8	26
8	To. S.	9	7	9/ 4	9/ 4	1.55	5.1	32
10	I. S.	10	9	5/15	6/ 4	3.25	6.6	16
Girls								
2	T. I.	4	10	11/29	11/20	1.50	4.6	35
4	T. K.	6	1	11/ 7	11/19	2.65	7.3	5
5	T. W.	6	10	10/ 9	10/10	1.55	5.4	20
6	S. M.	8	1	10/ 5	10/ 3	2.60	6.1	17
7	T. T.	8	4	11/23	11/23	2.40	4.8	73
8	Te. K.	8	6	7/14	7/ 2	2.00	5.8	24
9	S. K.	8	10	11/23	11/19	3.35	5.1	22
10	H. H.	8	11	11/22	11/23	3.15	5.7	12
11	F. M.	9	11	10/23	11/ 5	3.75	6.9	12
12	Se. N.	10	1	5/22	6/20	5.60	10.1	34
13	M. S.	10	3	10/30	11/ 5	3.35	6.1	96
14	K. T.	10	11	12/ 4	12/ 3	5.15	8.6	143
15	S. S.	11	2	5/15	4/ 3	4.55	5.9	78

* Age at the beginning of the experiment.

tion of heat was about 30 calories, but in the girls the rate of increase was found to be more conspicuous at the ages of 11 and 12 years, perhaps because of the influence of the more rapid growth during puberty.

Throughout the year the total production of heat increased not gradually but with seasonal variations. The maximum and minimum total amounts of heat produced are shown in table 5. Since the basal metabolic rate of children increases in relation to the rate of growth, it is not always correct to assume that the basal metabolic rate is high in January and low in July, as is the case in adults. However, as most of the children were first studied after September, the results show conclusively that as a rule the rate is high in January and low in July. However, children grow in height faster in May, June and July and slower in September, October and November. As to the gaining of weight, the rate is high in October, November and December but low

TABLE 5.—*Number of Maximum and Minimum Metabolic Rates Arranged According to Month*

	Number of Experiments	Maximum Metabolic Rates		Minimum Metabolic Rates	
		Number	Percentage	Number	Percentage
January	10	9	90	..	..
February	7	2	29	..	..
March	9	..	..	1	11
April	9	2	22	..	..
May	15	..	..	2	13
June	8	..	..	2	25
July	15	..	..	6	40
August	3	..	..	1	33
September	21	1	5	4	19
October	11	..	..	2	18
November	24	3	13	2	8
December	10	4	40	1	10

in June, July and August, being especially low in July. Therefore, the basal metabolic rate is correlated more closely with the rate of increase in weight than with that of the increase in height, and a loss of appetite and a decrease in weight in summer will be partly reflected by a decrease in the metabolic rate.

The average mean and percentage rate of deviation in the total amount of heat produced during a year varies only about 5 per cent (table 6).

The correlation between the total amount of heat produced and various physical factors (body weight, height and surface area) had been studied previously and the results published [1] showed that the weight of a child is a better criterion of the basal heat production than the body surface. Table 7 shows that each of the physical factors studied in the present experiments has a close relation to the basal heat production, and that the amount of heat produced and the weight are most closely correlated in these children. In this connection it must be recalled that during the period of growth the factors of age, weight

and height are closely related, much more so than is the case in adults. Adults weighing 60 Kg. are much more likely to vary in height than children weighing 20 Kg. Similarly, adults weighing 60 Kg. may vary in age from early youth to old age, but the variation in the age of boys

TABLE 6.—*Average Mean, Standard Deviation and Coefficient of Variation of Total Amount of Heat Produced During One Year*

		Average Mean	Standard Deviation	Coefficient of Variation
Boys				
No.	Name			
1	S. N.	844 ± 215.2	50.0 ± 9.01	5.92 ± 1.067
3	M. S.	1043 ± 265.9	58.6 ± 10.56	5.62 ± 1.013
4	K. M.	910 ± 232.0	34.0 ± 6.13	3.74 ± 0.674
5	Ma. S.	947 ± 241.4	49.9 ± 9.00	5.27 ± 0.950
6	T. S.	1081 ± 275.6	61.9 ± 11.16	5.73 ± 1.033
7	Y. I.	1002 ± 275.9	32.9 ± 6.41	3.28 ± 0.639
8	To. S.	1094 ± 278.9	34.1 ± 6.15	3.12 ± 0.562
10	I. S.	1296 ± 330.4	61.3 ± 11.05	4.73 ± 0.853
Girls				
2	T. I.	766 ± 210.9	29.6 ± 5.76	3.86 ± 0.752
4	T. K.	919 ± 253.1	62.3 ± 12.13	6.78 ± 1.320
5	T. W.	903 ± 230.2	25.2 ± 4.54	2.79 ± 0.503
6	S. M.	889 ± 226.6	61.6 ± 11.10	6.93 ± 1.249
7	T. T.	961 ± 252.6	44.0 ± 7.93	4.58 ± 0.826
8	Te. K.	989 ± 252.1	33.5 ± 6.04	3.39 ± 0.611
9	S. K.	1026 ± 261.6	41.0 ± 7.39	4.00 ± 0.721
10	H. H.	1006 ± 256.5	34.9 ± 6.29	3.47 ± 0.626
11	F. M.	952 ± 242.7	25.3 ± 4.56	2.66 ± 0.480
12	Se. N.	1095 ± 279.2	57.8 ± 10.42	5.28 ± 0.952
13	M. S.	1103 ± 281.2	28.5 ± 5.14	2.58 ± 0.465
14	K. T.	1002 ± 255.4	49.5 ± 8.92	4.94 ± 0.891
15	S. S.	1152 ± 317.2	47.6 ± 9.27	4.13 ± 0.804

TABLE 7.—*Correlation Coefficient Between the Total Amount of Heat Produced and the Weight, Height and Body Surface*

	Boys (67)	Girls (95)
Weight	0.8984 ± 0.0159	0.8607 ± 0.0179
Height	0.8495 ± 0.0229	0.8417 ± 0.0202
Surface area		
Takahira's formula *	0.8828 ± 0.0182	0.8675 ± 0.0171
Du Bois formula †	0.8813 ± 0.0184	0.8447 ± 0.0198
Lissauer's formula, modified by Talbot ‡	0.8945 ± 0.0165	0.8336 ± 0.0211

* Takahira, H.: The Basal Metabolism of Normal Japanese Men and Women, Rep. Imp. Gov. Ist. Nutrition **1**: 1 (Jan.) 1925.

† Du Bois, E. F.: Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1927.

‡ Czerny, A., and Keller, A.: Des Kindes Ernährung, ed. 2, Vienna, Franz Deuticke, 1825, vol. 1, p. 876.

weighing 20 Kg. is much smaller. It is thus probable that the weight of children automatically includes the variations in age and height and that all the physical factors have about the same relationship to the basal heat production. For practical purposes, therefore, and until a better unit has been devised, the weight should be taken as most nearly expressing the basal heat production of children.

SUMMARY

The basal metabolism of twenty-six children, aged from 3 years and 10 months to 11 years and 2 months, was studied every other month throughout a year and the following conclusions were reached:

1. In children there is an increase of about 30 calories in the total amount of heat produced annually. In girls, however, there is a higher rate of increase at the ages of 11 and 12 years, perhaps due to the influence of the increased rate of growth at puberty.

2. The amount of heat produced does not increase gradually throughout the year, but shows seasonal variations, the maximum amount being produced during January and the minimum during July. Most children decrease in weight during July. Therefore, a loss of appetite is expressed partly in terms of a decrease in the basal metabolic rate.

3. The amount of heat produced by one child deviates only slightly at different times during a year.

4. The coefficients of correlation between the basal heat production and the weight, height and surface area have been calculated, using 162 sets of data, and it has been demonstrated that the weight in the case of children is the most reasonable and practical factor for expressing the basal heat production.

CARBOHYDRATE METABOLISM

III. RELATION OF SALT AND WATER TO THE OXIDATION OF DEXTROSE

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AND
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DETROIT

When a number of years ago we noticed the failure of oxidation of dextrose injected intravenously into children recovering from attacks of vomiting, a series of experiments was planned to evaluate several of the factors which might be related to this phenomenon. Prominent among these were starvation, with the attendant depletion of glycogen stores, alterations in the acid-base balance of the blood and abnormalities in the water balance. In a previous communication [1] the effects of starvation and diminished stores were described. It was shown not only that there was no oxidation of the dextrose injected into persons in a state of complete starvation, since the sugar administered was stored, but that in persons in a submaintenance or partially depleted state storage took precedence over oxidation for purposes of accumulating energy and oxidation apparently did not occur until the stores were filled.

The present communication is concerned with an evaluation of the effects of changes in the reaction and the water content of the blood induced by the administration of various salts and water on the oxidation of dextrose administered intravenously while controlling so far as possible the presumed glycogen content of the liver, as reflection in the available dextrose of the basal metabolic mixture.

REVIEW OF THE LITERATURE

Various aspects of the problem have previously been approached from a number of angles, and in summary the following facts seem established: 1. The blood sugar rises following the administration of acid and remains normal or diminishes after the administration of

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From the Departments of Pediatrics and Laboratories, Henry Ford Hospital.

Read in abstract before the Society for Pediatric Research, Atlantic City, N. J., May 15, 1934.

1. Johnston, J. A.: Carbohydrate Metabolism: I. Effect of Previous Diet on Utilization of Glucose Injected Intravenously, Am. J. Dis. Child. **46**:309 (Aug.) 1933.

alkali.[2] 2. Acetone bodies have been produced in normal persons by the administration of soda and by hyperventilation and have been diminished by the administration of acid.[3] This seems also to be true in animals.[4] There is a lack of agreement on the effect of alkali when given to a person whose metabolism is already abnormal. Mosenthal and Killian [5] reported a decrease in acetone in the blood and a fall in the blood sugar with the administration of alkali to diabetic patients. In the case of one of their patients in the early stages of diabetic coma who was being treated with insulin, Bock, Field and Adair [6] attributed the failure to respond to the presence of large amounts of unidentified organic acid and expressed the belief that this situation indicated the need for soda. They urged its use in the first hours and days of treatment of every patient in diabetic coma. Hartmann and Darrow [7] made out an excellent case for the use of alkali in the treatment of persons in diabetic coma, and the end-results in their series of cases would seem to bear out their contention. Kydd [8] gave a good review of the status of the salt-and-water question in diabetic acidosis and stated (emphasizing the

2. Underhill, F. P.: Studies in Carbohydrate Metabolism, J. Biol. Chem. **25**:463 (July) 1916. Peters, J. P., Jr., and Geyelin, H. R.: Adrenalin Hyperglycemia, ibid. **31**:471 (Aug.) 1917. Hendrix, B. M., and McAmis, A. J.: Alkalosis Produced by Injections of Hydrazine Sulfate in Dogs, ibid. **61**:45 (Aug.) 1924. Koehler, A. E.: Effect of Acidosis on Sugar Metabolism, ibid. **67**:xlv, 1926.

3. Haldane, J. B. S.: Experimental and Therapeutic Alterations of Human Tissue Alkalinity, Lancet **1**:537 (March 15) 1924. Davies, H. W.; Haldane, J. B. S., and Kennaway, E. L.: Experiments on Regulation of the Blood Alkalinity, J. Physiol. **54**:32 (Aug.) 1920. Porges, O., and Lipschütz, H.: Ueber Azetonurie und Alkalose, Arch. f. exper. Path. u. Pharmakol. **97**:379, 1923. Beumer, H., and Soecknick, A.: Organic and Inorganic Acidosis, Ztschr. f. Kinderh. **37**:236, 1924. Booher, L. E., and Killian, J. A.: Ketosis Associated with Conditions of Alkalosis, Proc. Soc. Exper. Biol. & Med. **21**:528, 1924. Hubbard, R. S., and Wright, F. R.: Effect of Ingestion of Small Amount of Sodium Bicarbonate upon Excretion of Acetone Bodies, Ann. Clin. Med. **3**:634 (April) 1925. McQuarrie, I., and Keith, H. M.: Experimental Study of Acid-Base Equilibrium in Children with Idiopathic Epilepsy, Am. J. Dis. Child. **37**:261 (Feb.) 1929.

4. Wigglesworth, V. B.: Studies on Ketosis, Biochem. J. **18**:1203, 1924. Levine, H., and Smith, A. H.: Studies on Ketosis in Rat, J. Biol. Chem. **75**:1 (Oct.) 1927.

5. Mosenthal, H. O., and Killian, J. A.: Influence of Alkali Therapy on Ketosis in Diabetes Mellitus, J. Biol. Chem. **55**:xl, 1923.

6. Bock, A. V.; Field, H., Jr., and Adair, G. S.: Acid-Base Equilibrium in Diabetic Coma, Being a Study of Five Cases Treated with Insulin, J. Metab. Research **4**:27 (July-Aug.) 1923.

7. Hartmann, A. F., and Darrow, D. C.: Chemical Changes Occurring in the Body as a Result of Certain Diseases: Composition of Plasma in Severe Diabetic Acidosis and Changes Taking Place During Recovery, J. Clin. Investigation **6**:257 (Oct.) 1928.

8. Kydd, D. M.: Salt and Water in Treatment of Diabetic Acidosis, J. Clin. Investigation **12**:1169 (Nov.) 1933.

importance of sodium chloride): "Although it may be desirable to give sodium bicarbonate or a substitute, this salt will not furnish all the requirements of the depleted body fluids . . . clinical improvement parallels the restoration of body fluid and total ionic concentrations rather than the replacement of individual ions." In all this work it would seem most important to distinguish sharply between the effects of alkali when given to a normal person and when given to a patient with acidosis; in the one case an abnormal alkalotic state is being induced while in the other the resultant state is an approach to normal.

3. Since anything which affects the rate of glycogenolysis will in turn influence the oxidation of administered dextrose the known facts on this process are pertinent to this study. Liver glycogen has been shown to be diminished with acid and increased with alkali.[9] The process of glycogenolysis has been shown to be optimal on the acid side of neutrality;[10] Langfeldt[10a] expressed the belief that the diastatic ferment of the liver forms compounds with both phosphates and chlorides which vary in their glycogenolytic activity with the p_H of the medium but that physiologically the chloride-diastase complex is more important.

4. Some evidence suggests that dehydration enhances the effect of insulin (Joslin;[11] Andrews[12]) and in this connection it should be recalled that dehydration produced by dry diets and the withholding of water is identical with that induced by acid-producing salts (Schoenthal[13]). The findings of Schiff and Choremis,[14] however, seem at first glance to be difficult to reconcile with this idea. Comparing the effect of high and low intake of water on the fall of infants' blood sugar with starvation, they reported a failure of the blood sugar to fall when fluid was restricted and interpreted this as evidence of diminished ability to

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9. Bonanno, M., and Costa, A.: Azione di una dieta acidosica e di una dieta alcalosica sul ricambio carboidrato e sul ricambio energetico del coniglio, Pathologica **24**:854 (Dec. 15) 1932.

10. (*a*) Langfeldt, E.: Blood Sugar Regulation and Origin of Hyperglycemias: Conditions of Action of Liver Diastases, J. Biol. Chem. **46**:391 (April) 1921. (*b*) Cammidge, P. J., and Howard, H. A. H.: Influence of Insulin upon Activity of Diastatic Ferment of Liver, J. Metab. Research **5**:95 (Jan.-March) 1925. (*c*) Macleod, J. J. R.: Carbohydrate Metabolism and Insulin, New York, Longmans, Green & Company, 1926, p. 149.

11. Joslin, E. P.; Gray, H., and Root, H. F.: Insulin in Hospital and Home, J. Metab. Research **2**:651 (Nov.-Dec.) 1922.

12. Andrews, E.: Water Metabolism: Sugar Metabolism in Dehydration, Arch. Int. Med. **38**:136 (July) 1926.

13. Schoenthal, L.: Acid-Base Metabolism: Effects of Administration of Salt and of Restriction of Water, Am. J. Dis. Child. **37**:244 (Feb.) 1929.

14. Schiff, E., and Choremis, C.: Zur Pathogenese der Ernährungsstörungen beim Säugling; experimentelle Exsikkose und Kohlenhydratstoffwechsel, Jahrb. f. Kinderh. **114**:42 (Sept.) 1926.

utilize the sugar as a result of dehydration. The giving of alkali did not change the phenomenon, which likewise was associated with acetonuria, but insulin corrected it. Here again some consonance might result from another explanation: The dehydration might have accelerated glycogenolysis and so more rapidly (particularly in infants) have led to "starvation diabetes." Thus while the initial effect might be that of acceleration, the ultimate result would be depression, which would be caused by quite another phenomenon.

5. Tolerance curves have been shown to be of the "high prolonged," so-called diabetic type with acid [15] and to be little altered with alkali. The inference that this type of curve implies diminished oxidation is somewhat gratuitous; the high values for blood sugar were not associated with glycosuria and no quotients were given, so it cannot be deduced that a diminution in oxidation occurred.

METHODS AND OBSERVATION

Direct measurements of the process by means of respiratory quotients have been few because the carbon dioxide in the expired air is not an accurate measure of oxidation in the presence of a shifting reaction in the plasma; thus, measurements made during the process of recovery from acidosis are subject to the correction for displaced carbon dioxide. Since Shaw's [16] data for making this correction have been available it is possible to measure the effect on the oxidation process of the introduction of various ions.

Details of the technic are given in the first paper of this series.[1] Briefly, determinations on metabolism were made under basal conditions on subjects who had been on fixed diets for a number of weeks; dextrose was then injected intravenously and observations on the metabolic rate were repeated one, two and three hours after the injection, quotients being calculated on an hourly basis from eight to ten minute tests. From these and calculations of the urinary nitrogen the metabolic mixture was calculated according to the data of Lusk.[17]

The dextrose oxidation curves were plotted as follows: The first point, basal, indicates the number of grams of carbohydrate being oxidized in the basal hour calculated from the nonprotein respiratory quotient; the second, third and fourth points in the curve represent the amount being oxidized one, two and three hours following the intravenous injection of dextrose. In some experiments the salts were administered over a period of several days and curves for the respiratory quotient following the administration of dextrose were obtained after this period. Because of the variable induced by the fact that anything that tended to accelerate oxidation also tended to deplete stores and to give rise to a secondary depression of oxidation as a result of this depletion, other studies were made introducing the salts in the hour between the control quotient and the administration of the sugar.

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15. Thompson, G.; Mitchell, D. M., and Kolb, L. C.: Influence of Variations in Systemic Acid-Base Balance upon Carbohydrate Tolerance in Normal Subjects, Biochem. J. **27**:1253, 1933.

16. Shaw, L. A.: Comparative Capacity of Blood and of Tissue to Absorb Carbonic Acid, Am. J. Physiol. **79**:91 (Dec.) 1926.

17. Lusk, G.: Animal Calorimetry: Analysis of Oxidation of Mixtures of Carbohydrate and Fat, J. Biol. Chem. **59**:41 (Feb.) 1924.

When an acid or alkaline salt was administered determinations of the carbon dioxide content of the plasma were made basally, at the end of the hour of administration of saline solution (i. e., immediately before the injection of the dextrose) and finally at the conclusion of the determination of the third quotient. The quotients were then corrected in the manner suggested by Peters and Van Slyke[18] based on the data of Shaw.[16] With sodium chloride this was usually not done, for though with this salt there is a slight fall in carbon dioxide content the correction usually proved to be negligible.

EXPERIMENT 1 (Table 1, Chart 1).—The subject, H. M., a normal girl 12 years old, was given a measured diet for over a month preceding the observations. The basal respiratory quotients were all within a reasonable range. Ammonium chloride and sodium bicarbonate in amounts recorded in table 1 were ingested in the hour following the basal measurement. At the end of this time measurements

TABLE 1 (Experiment 1).—*The Effect of Ammonium Chloride and Sodium Bicarbonate on the Oxidation of Dextrose*

Time	Calories per Hour	Non-protein Respiratory Quotient	Carbohydrate Oxidized Gm. per Hour	Blood Sugar, Mg. per 100 Cc.	Carbon Dioxide Content, Vol. %	p_H	Water Intake: 7 A.M. to 1 P.M. Cc.	Output of Urine: 7 A.M. to 1 P.M. Cc.	Comment
B*	45.98	0.84	3.92	84	....	....	350	950	Control
1	46.74	0.90	5.70						
2	45.95	0.85	4.54						
3	46.65	0.81	3.52						
B*	45.59	0.824	4.07	119	58.9	7.33	600	1,172	6 Gm. ammonium chloride was ingested one hour before dextrose was injected
				112†	52.2	7.34			
1	45.57	0.915	6.26						
2	42.89	0.95	6.68						
3	44.03	0.796	2.67	95	49.9	7.32			
B*	46.94	0.804	3.09	106	60.8	7.50	600	749	18 Gm. sodium bicarbonate was ingested one hour before dextrose was injected
1	.....	....	....	86†	76.5	7.57			
1	48.66	0.92	7.02						
2	48.22	0.845	4.56						
3	46.12	0.73	0.76	103	75.2	7.50			

* In this and the succeeding tables B refers to the basal hour and 1, 2 and 3, to the hours following the injection of dextrose.

† This set of observations was made one hour after the particular salt being studied had been ingested and immediately preceding the injection of the dextrose.

were made of the carbon dioxide of the plasma and dextrose was injected. Observations on the metabolic rate were then repeated one, two and three hours thereafter. At the conclusion, measurements of the constituents of the blood were repeated.

The effect of ammonium chloride was definitely to increase oxidation; the peak of the oxidation curve was prolonged into the second hour.

Following the ingestion of sodium bicarbonate oxidation of carbohydrate was practically eliminated in the third hour, but in the first hour it was slightly increased over normal. It is possibly significant in this connection that the figures for the water intake and urinary output did not show in this experiment as great a relative retention of water with alkali as in subsequent experiments. The output was slightly greater than the intake; with acid the output was almost twice as great as the intake.

No significant change was noted in the blood sugar following the ingestion of acid; following the ingestion of alkali the blood sugar was definitely reduced.

18. Peters, J. B., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 56.

There was demonstrated here a diminution in oxidation with alkali and an increase with acid. A possible correlation of these phenomena with water exchange will be referred to later.

EXPERIMENT 2 (Table 2, Charts 2 and 3).—The subject, A. K., a normal girl 12 years old who had been gaining weight satisfactorily on a measured diet for several weeks prior to the beginning of the experiment, was given ammonium chloride and sodium bicarbonate by mouth in amounts recorded in table 2 throughout the days preceding each set of observations.

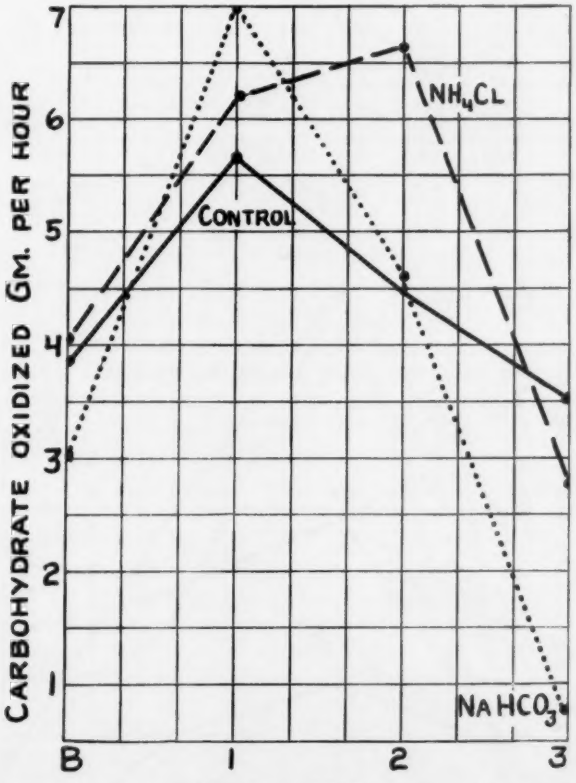

Chart 1 (experiment 1).—Dextrose oxidation curves showing the effect of ammonium chloride and sodium bicarbonate. In this and subsequent charts of dextrose oxidation curves the first point, *B*, is the number of grams of carbohydrate being oxidized in the basal hour, and points 1, 2 and 3 in the curve represent the amount being oxidized one, two and three hours following the intravenous injection of the indicated amount of dextrose given immediately after the basal run.

The initial effect of the acid was to increase both the basally oxidized carbohydrate and that oxidized following the injection of dextrose intravenously.

With a shift to alkali both the basal carbohydrate content and the amount oxidized following the injection of dextrose fell. When, however, the alkali was administered for an additional two days there was a return to normal or even an increase beyond normal.

TABLE 2 (Experiment 2).—*The Effect of Ammonium Chloride and Sodium Bicarbonate on the Oxidation of Dextrose*

Date	Time	Calories per Hour	Non-protein Respiratory Quotient	Carbohydrate Oxidized per Hour, Gm.	Blood Sugar, Mg. per 100 Cc.	Carbon Dioxide Content, Vol. %	*pH*	Basal Metabolic Mixture, Percentage of Calories			Comment
								Protein	Fat	Carbohydrate	
1/28	B	54.4	0.81	3.82	..	58.9	7.41	22	49	29	
	1	50.3	0.84	4.55							
	2	51.4	0.815	4.08							
	3	52.9	0.79	3.38							
2/10	B	51.7	0.86	5.86	84	50.2	7.35	16	38	46	15 Gm. ammonium chloride on 2/9
	1	54.07	0.92	8.19							
	2	50.71	0.87	6.21							
	3	52.14	0.805	3.78	..	52.1					
2/12	B	49.48	0.82	3.92	75	43.8	7.25	20	47	33	20 Gm. ammonium chloride on 2/11
	1	51.18	0.90	5.89							
	2	47.84	0.89	5.29							
	3	50.36	0.84	4.96	..	46.5					
2/15	B	51.47	0.75	1.49	81	66.6	7.44	22	66	12	60 Gm. sodium bicarbonate on 2/13 and 2/14
	1	52.87	0.84	4.69							
	2	47.62	0.75	1.43							
	3	53.40	0.765	2.28	..	65.6	7.43				
2/17	B	51.93	0.80	3.61	57	63.7	7.47	17	55	28	80 Gm. sodium bicarbonate on 2/15 and 2/16
	1	56.48	0.905	8.10							
	2	52.70	0.835	5.10							
	3	54.91	0.80	3.85	..	61.6	7.44				

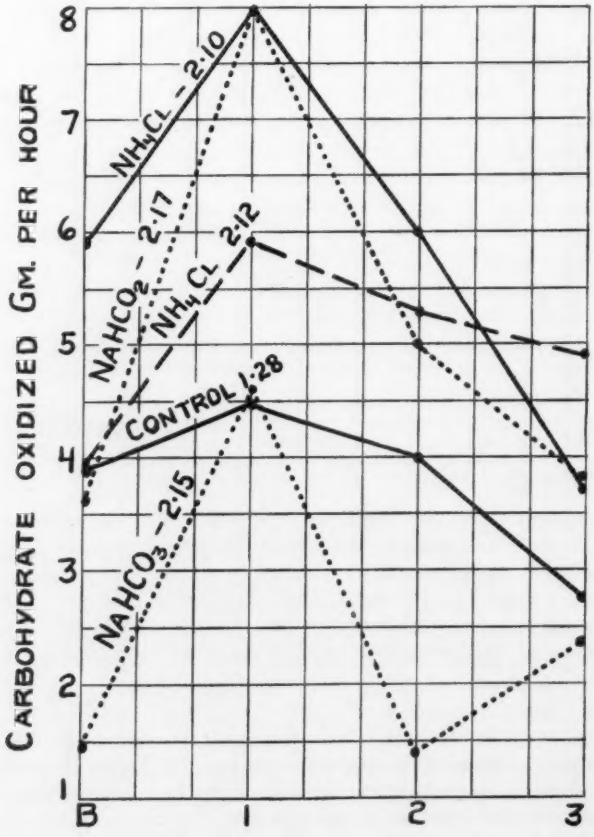

Chart 2 (experiment 2).—Dextrose oxidation curves following the administration of ammonium chloride and sodium bicarbonate.

There would seem to be a correlation between these findings and the water balance as approximated by a measurement of water intake and urinary output. These data are plotted separately in chart 3. The decrease in oxidation of carbohydrate occurred simultaneously with a sharp increase of water intake over urinary output (retention of fluid), and the increase with alkali took place at a

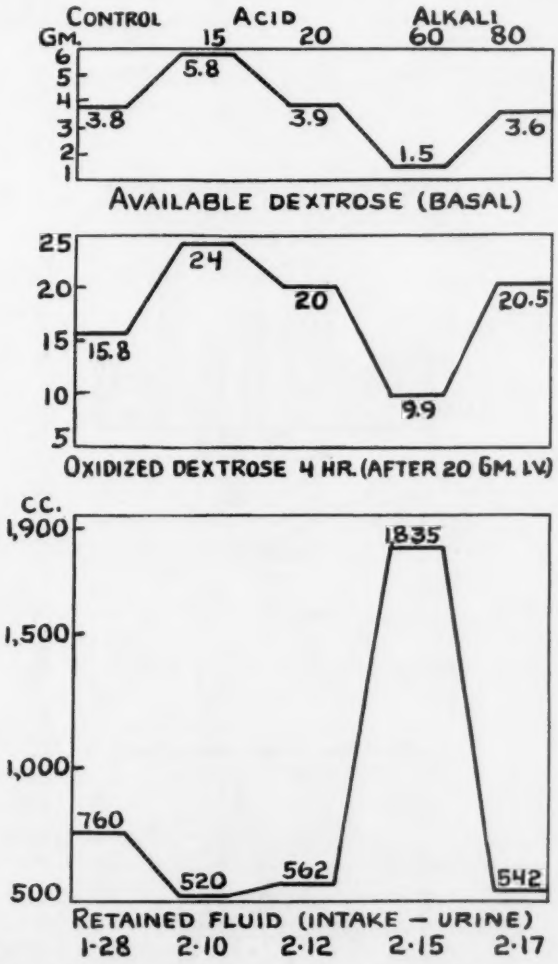

Chart 3 (experiment 2).—Curves showing the available basal dextrose, the oxidized dextrose four hours after the administration of 20 Gm. intravenously and the water balance during the period of the experiment.

time when gross diuresis was taking place and the difference between intake and output had become less than the control.

EXPERIMENT 3 (Table 3, Chart 4).—This subject ingested during two days prior to the observations 56 Gm. of sodium chloride in capsules. She was allowed to take as much water as she wished, and she drank during that time 12,495 cc. This was retained transiently, as will be seen in chart 4, and the second oxidation curve

TABLE 3 (Experiment 3).—*The Effect of Sodium Chloride and Water on the Oxidation of Dextrose*

Date	Time	Calories per Hour	Non-protein Respiratory Quotient	Carbohydrate Oxidized, Gm. per Hour	Basal Metabolic Mixture, Percentage of Calories			Comment
					Protein	Fat	Carbohydrate	
8/25	B	49.7	0.892	6.55	17	29	54	Control
	1	49.7	0.934	7.96				
	2	49.4	0.924	7.58				
	3	52.0	0.894	7.01				
8/30	B	49.6	0.795	3.18	17	57	26	22 Gm. sodium chloride and 6,220 cc. water on 8/28; 34 Gm. sodium chloride and 6,275 cc. water on 8/29
	1	52.9	0.870	5.19				
	2	52.1	0.980	10.22				
	3	52.1	0.860	5.66				
9/1	B	47.7	0.813	3.68	17	51	32	Details of water intake and urinary output as shown in chart 4
	1	46.6	0.808	3.42				
	2	46.5	0.887	5.94				
	3	47.6	0.817	3.79				

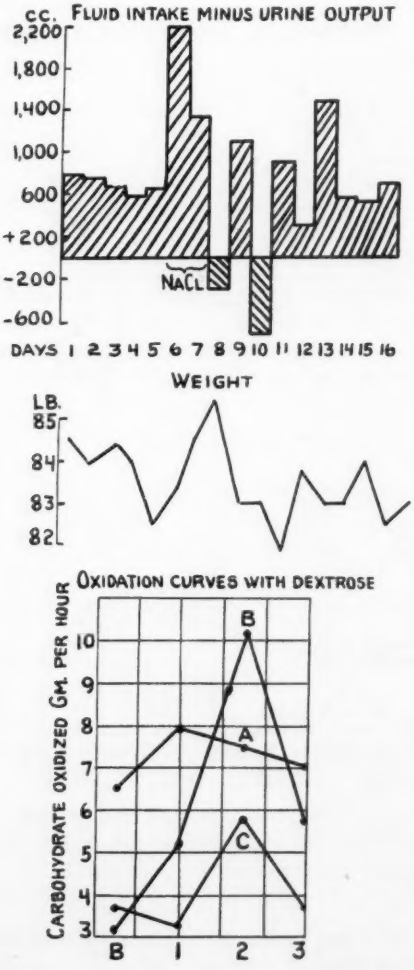

Chart 4 (experiment 3).—The effect of sodium chloride on dextrose oxidation, showing the fluid intake minus the urinary output, the variation of weight and the oxidation curves after the administration of dextrose. In the latter, *A* is the control curve on the third day of the experiment; *B*, the curve on the eighth day, and *C*, the curve on the eleventh day.

plotted was obtained during the time of release of this in the urine; on that day the urinary output exceeded the intake of water by mouth by 300 cc. The oxidation curve at this time showed a marked acceleration, which was both absolute and relative since the basal figure was quite low; ordinarily this would result in a flattening of the curve. Another control curve made three days later was the type seen for persons with depleted stores, and it is reasonable to infer that a sweeping out of glycogen occurred. The curve showed no response in the first hour.

So rapidly was sodium chloride eliminated that any estimation of the effect of its accumulation beyond normal limits had to be made with the technic involved

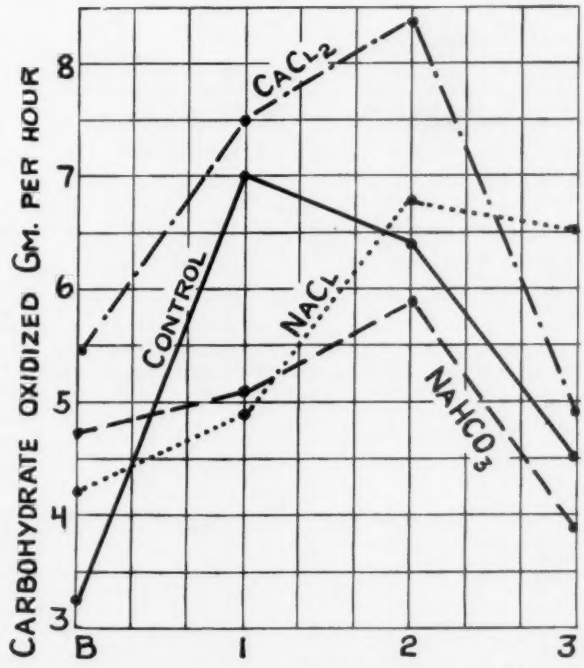

Chart 5 (experiment 4).—Dextrose oxidation curves following the administration of sodium chloride, calcium chloride and sodium bicarbonate.

in giving the salt in the hour following the basal determination. This was done in experiments 4, 5 and 6.

Experiment 4 (Table 4, Charts 5 and 6).—Following the administration of sodium bicarbonate there was a definite depression of the curve of oxidation. The carbon dioxide content rose from 50.9 to 59.7 volumes per cent. Relative hydration occurred during the time occupied by the experiment, 790 cc. of water being drunk while the urinary volume was but 490 cc. This was reflected in a slight fall in serum proteins. The depression of oxidation was relatively greater than was apparent from the actual number of grams of carbohydrate oxidized, for the basal carbohydrate was appreciably higher than that of the control period, and we have previously shown that, other factors being equal, the amount of dextrose oxidized will bear a direct relationship to this figure.

Calcium chloride caused a definite increase in the oxidation of sugar. The peak was reached in the second hour after the injection of dextrose rather than in the first period, as in the control. The full effect of this salt when taken by mouth was not attained at the end of an hour; at that time the carbon dioxide content had fallen from 50.2 to 42.6; at the conclusion of the three hour period it had fallen further to 32.6. Water intake and urinary volume were approximately equal. A slight fall in the serum protein suggested that water had been drawn into the plasma.

TABLE 4 (Experiment 4).—*The Effect of Sodium Bicarbonate, Calcium Chloride and Water on the Oxidation of Dextrose*

Time	Calories per Hour	Non-protein Respiratory Quotient	Carbohydrate Oxidized per Hour, Gm.	Blood Sugar, Mg. per 100 Cc.	Carbon Dioxide Content Vols. %	p_H	Serum Albumin, Gm.	Serum Globulin, Gm.	Water Intake, 7 A.M. to 1 P.M.	Urinary Output, 7 A.M. to 1 P.M.	Comment
B*	57.45	0.79	3.25	94	55	7.52	4.56	3.24	200	535	Control period
1	56.88	0.895	7.0								
2	56.85	0.877	6.4								
3	56.65	0.82	4.4								
B	58.53	0.815	4.61	80	50.9	7.92	5.63	2.61	790	490	16 Gm. sodium bicarbonate with 590 cc. of water given in 1 hour between basal observation and administration of dextrose
				72*	59.7	7.49	5.50	2.27			
1	57.88	0.83	5.16								
2	57.88	0.85	5.90								
3	57.12	0.80	3.87	73	56.0	7.50					
B	56.2	0.845	5.45	78	50.2	....	4.98	1.82	400	370	14 Gm. calcium chloride and 400 cc. of water in 1 hour between basal observation and administration of dextrose
				86*	42.6	....	4.86	1.70			
1	56.1	0.90	7.48								
2	53.9	0.935	8.35								
3	49.3	0.85	4.90	71	32.4	....	5.01	1.41			
B	56.18	0.827	4.20	78	56	....	6.36	2.51	1,800	1,800	3.3 Gm. sodium chloride with 1,000 cc. of water between basal observation and these determinations; during following 3 hours additional 2 Gm. sodium chloride with 800 cc. water
				67*	55	....	6.25	1.54			
1	55.09	0.855	5.02								
2	56.44	0.907	6.91								
3	55.21	0.902	6.53	73	51	....	5.75	1.92			

* This observation was made after the particular salt being studied had been ingested for one hour and immediately preceding the injection of the dextrose.

Sodium chloride caused a dual effect; there was in the first hour a definite lag in the curve of oxidation which then became accelerated and was prolonged into the third hour. Because this seemed related to hydration this experiment was charted separately against water intake and urinary output in chart 6. A large intake of water was transiently retained with the salt, and it was during this period that oxidation was retarded; coincidentally with the release of these substances in the urine the oxidation of dextrose is accelerated.

EXPERIMENT 5 (Table 5, Chart 7).—The ingestion of sodium chloride and water for two days prior to the experiment was followed by a striking increase in the oxidation of dextrose which had been injected.

In the experiment with alkali, sodium bicarbonate was given only on the morning of the determinations. There resulted a marked diminution in oxidation. The

TABLE 5 (Experiment 5).—*The Effect of Sodium Chloride, Sodium Bicarbonate and Water on the Oxidation of Water*

Time	Calories per Hour	Non-protein Respiratory Quotient	Carbohydrate Oxidized, per Hour, Gm.	Blood Sugar, Mg. per 100 Cc.	Carbon Dioxide Content, Vols. %	Water Intake, 7 A.M. to 1 P.M., Cc.	Urine Output, 7 A.M. to 1 P.M., Cc.	Comment
B	56.0	0.81	3.99	154	54.1	500	920	Control period
1	55.1	0.94	8.56					
2	56.8	0.87	6.33					
3	55.9	0.80	3.61					
B	54.6	0.78	3.22	92	53.5	600	1,055	After ingestion of 28 Gm. sodium chloride and 3,600 cc. water 2 days previously, and of 12 Gm. sodium chloride and 2,725 cc. water 1 day previously
1	55.8	0.99	10.70					
2	53.01	0.84	4.89					
3	53.5	0.79	3.15					
B	51.1	0.82	4.0	92 98*	54 66.6*	1,200	935	After one hour's administration of 18 Gm. sodium bicarbonate with 1,000 cc. water
1	49.76	0.89	5.97					
2	53.20	0.855	5.37					
3	54.16	0.81	3.69	85	63.6			

* This observation was made after the particular salt being studied had been ingested for one hour and immediately preceding the injection of the dextrose.

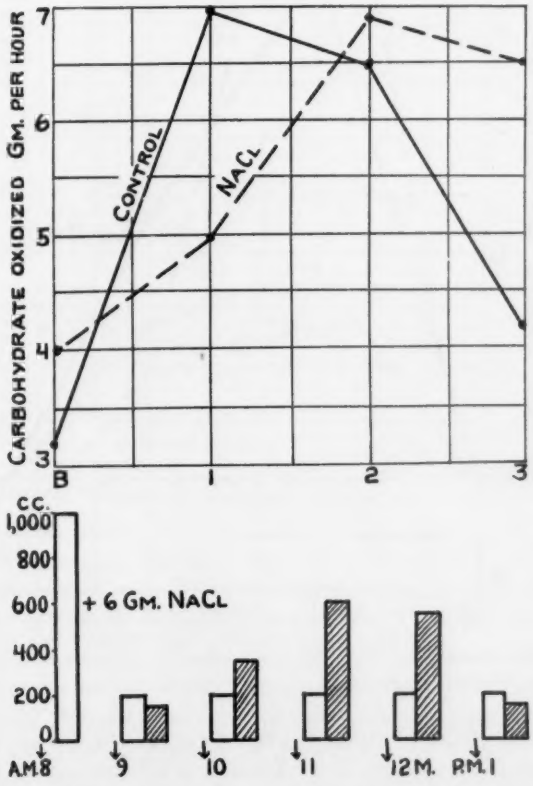

Chart 6 (experiment 4).—The effect of sodium chloride and water on the dextrose oxidation curve and a comparison of the fluid intake and urinary output. In the latter the open column indicates the intake of water with sodium chloride and the cross-hatched columns, the urinary output.

figures for water intake and urinary output throughout the four hours of the experiment showed a relative hydration with sodium bicarbonate and a definite loss of water from the body as a result of the administration of sodium chloride. After two days of sodium chloride and water, the albumin content of the serum had fallen from 8.05 to 7.83 mg. and the globulin content from 1.91 to 1.26 mg., suggesting dilution of the plasma.

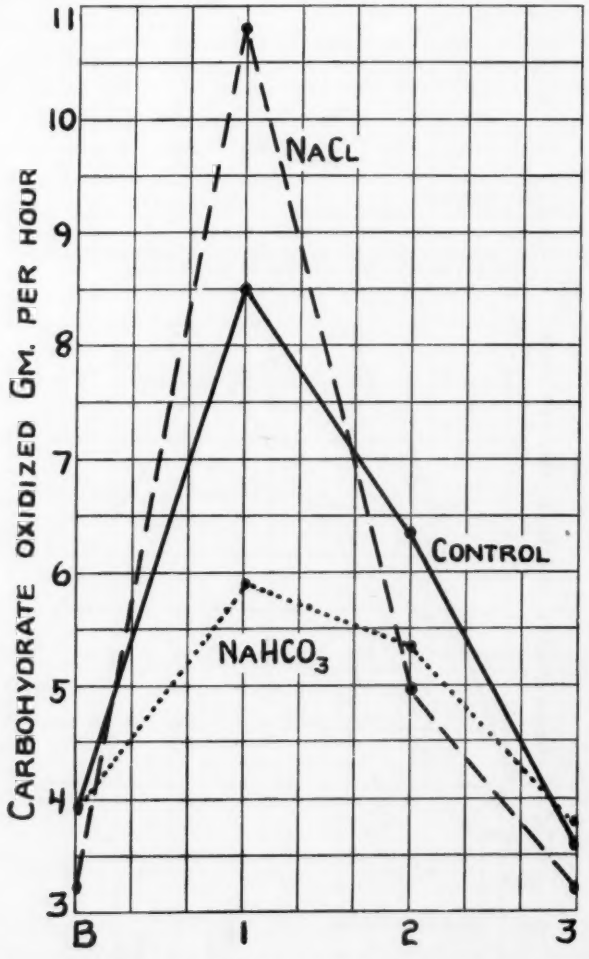

Chart 7 (experiment 5).—The effect of sodium bicarbonate and sodium chloride on the dextrose oxidation curves.

Experiment 6 (Table 6, Chart 8).—This set of observations was made to study the effect of salt in the presence of the depletion of glycogen known to be produced by the administration of thyroid. When such a state is induced by withholding food it would not, of course, be expected that subsequent alteration in p_H would affect the oxidation of administered dextrose in any way. This point was previously demonstrated [1] in the epileptic patient whose inability to oxidize the sugar administered after fasting was not improved when the carbon dioxide content was

raised by the administration of soda. The situation created here, however, permitted the continued intake of food while at the same time glycogenolysis was being increased by the administration of thyroid. As was previously shown,[19] the first effect of thyroid on carbohydrate metabolism was an acceleration of oxidation accompanying the increase in glycogenolysis; ultimately, the effect was suppression of oxidation as a result of depleted stores. These states were reflected in a falling carbohydrate curve in the basal metabolic mixture and a rising protein curve. Amounts of thyroid which may fail to give rise to an increase in the total rate will induce this effect on the metabolic mixture. When ammonium chloride was administered following thyroid the depressing effect on oxidation was accentuated.

TABLE 6 (Experiment 6).—*The Effect on Dextrose Oxidation of Sodium Bicarbonate and Ammonium Chloride Following the Administration of Thyroid*

Date	Time	Calories per Hour	Non-protein Respiratory Quotient	Carbohydrate Oxidized per Hour, Gm.	Blood Sugar, Mg. per 100 Cc.	Carbon Dioxide Content, Vols. %	Basal Metabolic Mixture, Percentage of Calories: Protein	Fat	Carbohydrate	Ratio*	Comment
8/3	B	55.9	0.83	5.09	102	....	15	48	37	3.5	Control
	1	54.4	0.896	7.46							
	2	52.9	0.825	4.59							
	3	49.4	0.73	0.84							
9/2	B	53.4	0.787	3.01	138	....	15	62	23	4.0	Thyroid (dried gland) 2 grains b. i. d. 8/5 to 8/29; 5 grains b. i. d. 8/29 to 9/1
	1	52.3	0.925	8.16							
	2	45.9	0.822	3.80							
	3	44.9	0.791	2.83							
9/14	B	43.5	0.778	1.95	420	43.5	24	58	18	2.0	2 weeks after discontinuing thyroid
	1	49.2	0.743	1.22							
	2	52.5	0.744	1.38							
	3	52.0	0.744	1.36							
9/16	B	51.1	0.72	0.45	160	18.6	31	65	4	1.3	30 Gm. ammonium chloride between observation on 9/14 and 9/16
	1	55.1	0.736	1.01							
	2	52.5	0.759	1.67							
	3	53.1	0.737	0.99							
9/20	B	47.7	0.776	2.66	122	68.4	9	68	23	4.0	36 Gm. sodium bicarbonate daily on 9/17, 9/18 and 9/19
	1	53.3	0.827	5.10							
	2	53.4	0.797	3.87							
	3	49.9	0.776	2.79							

* This figure was described in the first paper[1] as representing normally a constant relationship between the available dextrose and the amount oxidized following the injection of dextrose; an increase, therefore, is interpreted as accelerated oxidation and a decrease, as diminished burning.

The ingestion of sodium chloride was followed by a partial return of the curve of oxidation toward normal. There was an interesting change in the basal metabolic mixture following the administration of alkali, with the protein content falling strikingly and carbohydrate rising from 4 to 23 per cent.

These results might be interpreted in a manner similar to McLeod's explanation of the effect of acid and alkali on glycogenolysis, the effect of sodium chloride depending on the p_H of the plasma when it was administered; since optimal is probably slightly to the acid side of neutrality, a carbon dioxide content of 68.4 volumes per cent would be

19. Johnston, J. A.: Carbohydrate Metabolism: II. Rôle of the Thyroid Gland, Am. J. Dis. Child. **48**:1015 (Nov.) 1934.

closer to it than one of 18.6. Another explanation might be that during the several days of its administration a partial restoration of glycogen stores as reflected in the basal metabolic mixture was made possible by the presence of alkali and that it is the level of glycogen which immedi-

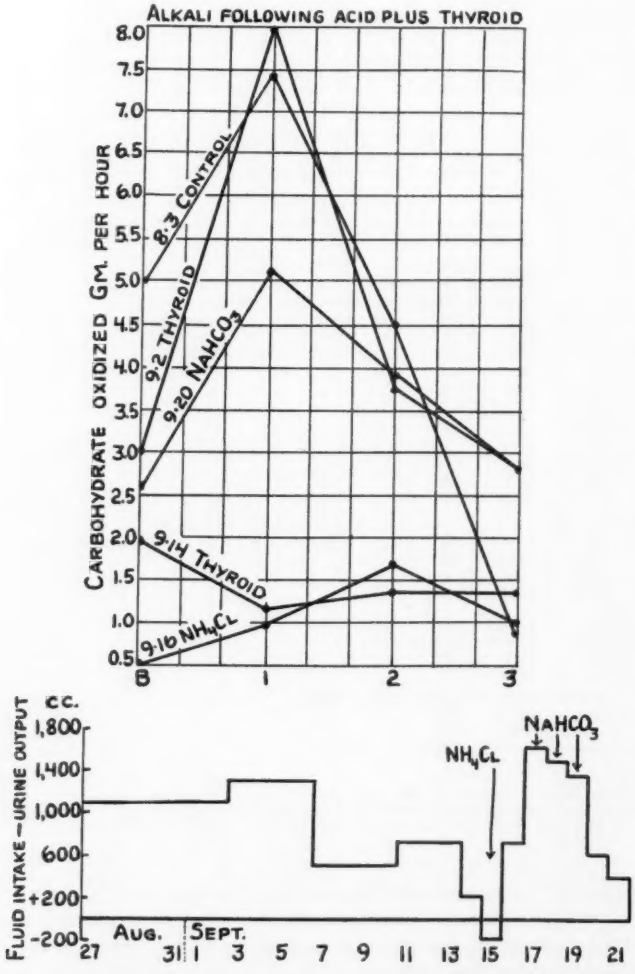

Chart 8 (experiment 6).—The effect of alkali on the dextrose oxidation curves following the administration of acid plus thyroid and the comparison of the fluid intake and urinary output showing the effect of the ingestion of ammonium chloride and sodium bicarbonate.

ately determines the fate of injected dextrose. In any case, the experiment was instructive in showing a totally different effect with acid and alkali in the presence of depleted stores from that obtained when these are normal.

COMMENT

These findings suggest that the facts established for the metabolism of glycogen are paralleled by similar ones on the oxidation of dextrose. With slight changes to the acid side the oxidation of carbohydrate is accelerated; when these changes are very great, oxidation is depressed. It is not clear whether this is a direct or an indirect effect, an initial acceleration resulting in a depletion of stores. When sodium chloride is administered to a normal person a transient depression is followed by an acceleration of oxidation. Likewise, although quite consistently the ingestion of a fairly large amount of sodium bicarbonate is followed by a diminution in oxidation, when a point is reached at which release of the ion takes place with coincident moving of water as judged by diuresis there is again evidence that oxidation is accelerated. There may be implicit in this Langfeldt's concept of a chloride-diastase complex, or it may be a simpler phenomenon involving the thought of dextrose being transported more rapidly when a situation is created which favors diuresis. These data do not furnish an explanation for the phenomenon. In any case, optimal oxidation of dextrose may be thought of as taking place slightly to the acid side of neutrality and slightly to the concentrated side of normal so far as hydration goes.

CONCLUSIONS AND SUMMARY

1. When acid and alkaline salts are administered to normal persons the oxidation of dextrose is accelerated on the acid side of neutrality and inhibited on the alkaline side.

2. When sodium chloride and water are taken by mouth by a normal person there is a transient depression of oxidation during the time that these substances are retained in the body, followed by an acceleration of oxidation when they are released.

3. When thyroid was administered there was evidence of depleted glycogen stores. Acid administered at this time was followed by a complete inhibition of an already diminished oxidation; alkali, by a partial return to normal.

Dr. O. H. Gaebler made the determinations of p_H and read the manuscript, and Dr. F. W. Hartman supervised the determinations of metabolism. Dr. Robert J. Mason assisted in preparing some of the patients.

DISCUSSION

Dr. Warren M. Sperry, New York: Is it possible that the increased carbon dioxide could be associated with a blowing off of carbon dioxide?

Dr. Joseph A. Johnston, Detroit: We thought that we had prevented this possibility by the method described by Peters and Van Slyke, based on the data of Shaw. The carbon dioxide content of the plasma is determined at the beginning of the experiment, again after the administration of the salt studied and finally at the end, and the quotient is corrected for retained or displaced carbon dioxide.

EOSINOPHILIA IN SCARLET FEVER

II. GENERAL CONSIDERATIONS

SAMUEL FRIEDMAN, M.D.
BOSTON

In a previous communication [1] a study of eosinophilia in scarlet fever was begun. In the present article I wish to report (1) observations on eosinophilia during the first week of illness; (2) the presence of a previously neglected phenomenon, namely, a secondary rise in the eosinophil count, and (3) the nature of the eosinophilia in scarlet fever.

METHODS AND MATERIAL

In eighty-five cases of scarlet fever, which is by far the largest series reported in the literature, eosinophil counts were made daily during the first week of illness and thereafter on alternate days (occasionally a two day interval was allowed to elapse). Blood smears were made by the slide method and stained with Wright's stain. Three hundred white cells were counted in determining the percentage of eosinophils. Only patients admitted to the hospital in an early stage of the disease, usually within a day of the appearance of the rash, were included in the series.

PRIMARY EOSINOPHILIA, DURING THE FIRST WEEK OF ILLNESS

In chart 1 is shown the typical course of the eosinophil count during the first week of the disease. During the acute illness of the first two or three days the eosinophil count was normal or, in severe cases, depressed; then, as the temperature descended and the condition of the patient was ameliorated, the eosinophil count began to rise. I shall refer to this rise as "primary eosinophilia." In the mildest cases eosinophilia was present by the time the patient was admitted to the hospital. In the first report it was stated that with a single examination of the blood eosinophilia was noted in 46 per cent of the cases. In this series, with repeated daily blood counts, eosinophilia was noted in 77.7 per cent of the cases during the first week of illness. The maximal counts attained are indicated in table 1.

In approximately one-half the cases, the peak was between 5 and 8 per cent, and the average in cases in which eosinophilia was observed was 7.7 per cent. Thus, from the standpoint of the maximal counts attained, my observations agree more closely with those of von Ambrus

1. Friedman, S.: Eosinophilia in Scarlet Fever: I. As a Diagnostic Aid, Am. J. Dis. Child. **49**:933 (April) 1935.

than with those of Markovitch and Guératovitch, who in thirty cases found the maximal count most frequently to approach 12 per cent of the total number of white blood cells.

Various factors affecting the height and frequency of eosinophilia will be discussed in succeeding communications.

The maximal count was usually noted about the fourth or fifth day of the illness in the milder cases and a day or two later in the cases of somewhat greater severity. In the more severe cases there was frequently no primary eosinophilia. The possible significance of this will be discussed later. After reaching a peak, the eosinophil count begins to descend, usually attaining a normal value by the eighth or ninth day of the illness.

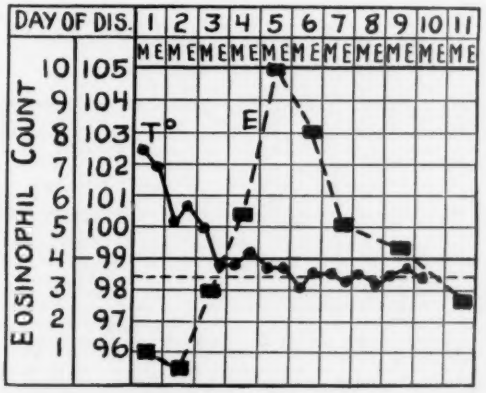

Chart 1.—Typical curves of the eosinophil count and the temperature during the first eleven days of illness. The solid line indicates the temperature and the broken line, the eosinophil count.

TABLE 1.—*Maximal Eosinophil Counts in Primary Eosinophilia of Scarlet Fever*

Maximal Eosinophil Count, Percentage	Number of Cases	Percentage of Total
Less than 4 (no eosinophilia)	19	22.3
4.1 to 6.0	25	29.5
6.1 to 8.0	17	20.0
8.1 to 10.0	13	15.3
10.1 to 12.0	6	7.1
12.1 to 14.0	3	3.5
Over 14.1	2	2.3

SECONDARY EOSINOPHILIA, DURING THE SUCCEEDING WEEKS OF ILLNESS

The presence of a second rise in the eosinophil count seems to have been almost entirely overlooked by previous investigators. Only Bix

mentioned it. He said: "Zwischen dem 8 bis 11 Tage weisen sie eine Senkung meistens bis zur Norm auf, um dann neuerlich wieder zusteigen." (Between the eighth and the eleventh day they show a reduction, usually to normal, after which they again increase in number.)

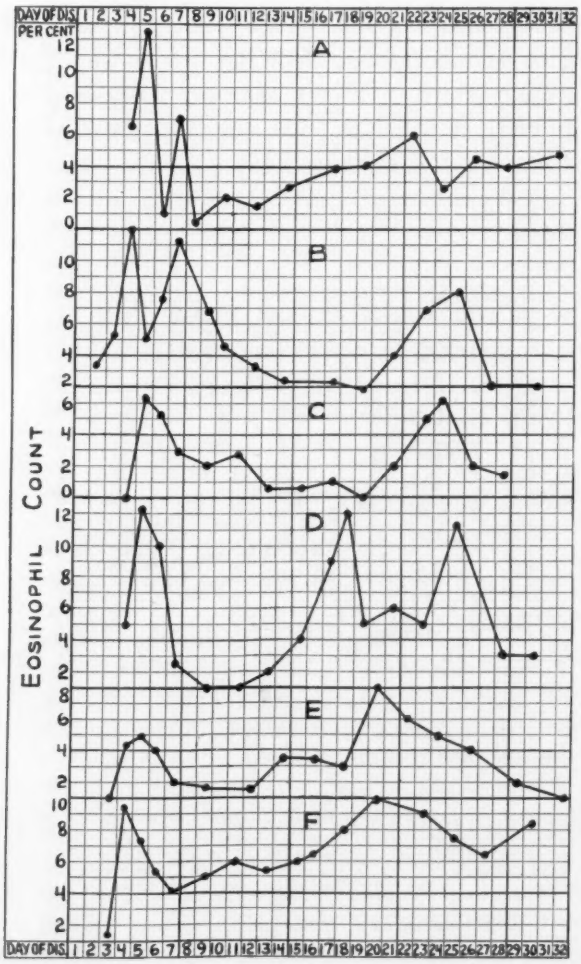

Chart 2.—Typical curves of the eosinophil count during four or five weeks of illness.

I have called this later rise in the eosinophil count "secondary eosinophilia."

Chart 2 depicts typical curves of the course of the eosinophil count during the four or five weeks of stay in the hospital. Chart 2 *F* represents a few cases in which the eosinophil count was raised during the

entire course of the disease, but even here one sees the distinct secondary elevation.

In this series of cases secondary eosinophilia was almost as constant a finding as the primary rise, being present in 72.9 per cent of the cases. Both a primary and a secondary rise were noted in the majority of cases; in 30.6 per cent either one or the other was noted, and in only 9.4 per cent was there no eosinophilia during the entire course of the disease (table 2).

In 90.6 per cent of the cases of this series eosinophilia was noted at some time during the four or five weeks of stay in the hospital. In a number of instances the absence of a secondary rise was probably attributable to the presence of complications. The maximal count attained during the secondary eosinophilia was at times higher than that during the primary rise and frequently extended over a longer period of time. A comparison of the maximal eosinophil counts attained during the primary and secondary stages is shown in chart 3.

TABLE 2.—*Incidence of Eosinophilia in Scarlet Fever*

Eosinophilia	Number of Cases	Percentage of Total
Primary and secondary	51	60.0
Primary	15	17.7
Secondary	11	12.9
None	8	9.4

It will be seen that the maximal counts during the secondary rise were almost equal to those attained during the primary eosinophilia. The average maximal eosinophil count during the secondary eosinophilia was 7.3 per cent as compared with 7.7 per cent for the primary rise. I found the onset of the secondary eosinophilia to occur much later than Bix stated. In my series the secondary eosinophilia began most frequently about the twenty-second day of the illness, and the earliest onset was on the fifteenth day. Eosinophilia was frequently present when the patient left the hospital and one patient demonstrated the phenomenon on the fifty-sixth day of the stay in the hospital.

A composite curve of the course of the eosinophilia in a mild case of scarlet fever obtained by plotting the eosinophil counts obtained in approximately sixty mild cases is shown in chart 4. Similar composite curves for the moderately severe and the severe cases cannot be presented as the number of such cases is still relatively small.

COMMENT

While there remain a number of factors to be investigated, I believe that a preliminary discussion of the nature of the eosinophilia in scarlet

fever would be of advantage. Previously, attention has been divided chiefly between two explanations of this phenomenon. The first is that the eosinophilia is part of an allergic or anaphylactic picture, and the

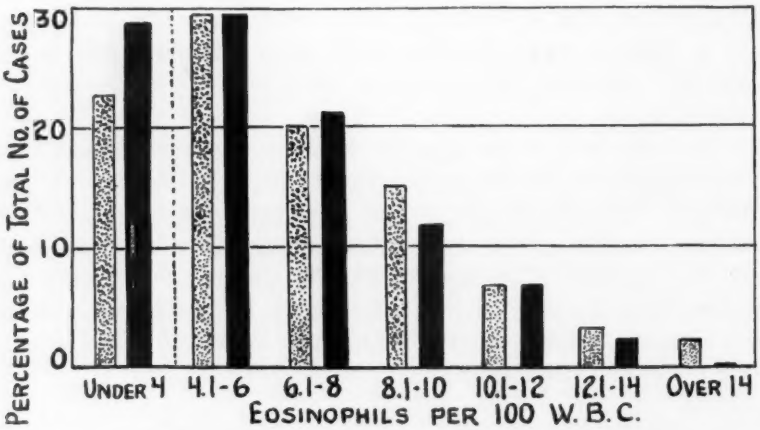

Chart 3.—A comparison of the maximal eosinophil counts during primary and secondary eosinophilia. The stippled columns indicate primary eosinophilia and the solid columns, secondary eosinophilia.

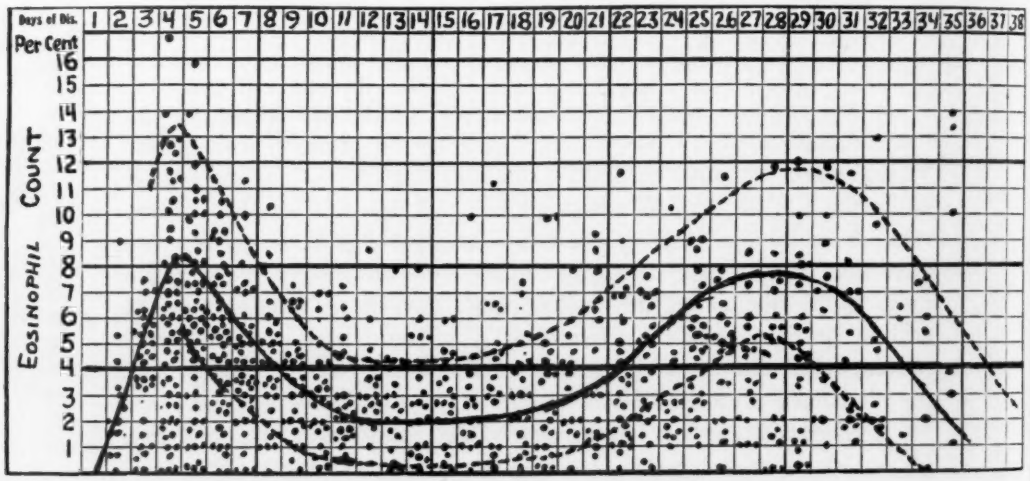

Chart 4.—A composite curve of the eosinophil count in mild scarlet fever obtained by plotting the eosinophil counts in approximately sixty mild cases.

proponents of this theory offer the presence of eosinophilia as evidence in favor of the allergic pathogenesis of scarlet fever.[2] The conception

2. Meyer, S.: Der Scharlach als anaphylactisches Phänomen, Deutsche med. Wchnschr. **49**:509 (April 20) 1923.

of scarlet fever as an allergic disease and the eosinophilia as part of an allergic entity has little to recommend it thus far. The other theory, supported by Naegeli [3] and Bix,[4] explains the eosinophilia as a direct consequence of the exanthem, which exerts a specific chemotaxis for eosinophils. As partial proof of this theory, Bix offered the observation that in cases in which there is the most intense rash the highest eosinophil counts are seen. Apparently, however, he based this conclusion on observations on a few isolated cases. Observations during the course of the present investigation cast a good deal of doubt on Bix' conclusion. In order definitely to settle this rather important question, I have analyzed the results in one hundred cases of scarlet fever (eighty-five cases in the present series and fifteen cases in a new series). The cases were divided according to the degree of intensity of the exanthem on the patient's admission, as follows:

Type of Rash	Grade
Very mild	1
Mild	2
Moderate	3
Bright	4
Intense	5

The maximal eosinophil count attained in each case (referring now only to the primary eosinophilia, which is the basis of Bix' comparison and which is obviously the only eosinophilia to which the rash can be related) was compared with the degree of exanthem which was demonstrated. The results are presented in table 3 and chart 5.

It is apparent at a glance that the patients with the more intense rashes did not show the highest eosinophil counts; if anything, the tendency was distinctly in the opposite direction. The significance of this will be discussed more fully in a later report. Thus, Bix' conclusion, based on inadequate data, is definitely erroneous and cannot be used as evidence in favor of Naegeli's theory of the nature of the eosinophilia in scarlet fever.

However, the greatest objection to attributing the eosinophilia either to allergy or to the exanthem arises from the presence of the secondary eosinophilia which has been demonstrated conclusively in this study. How can one explain the secondary rise in the eosinophil count, which occurs three weeks after the onset of illness, on an allergic basis? While the theory that the exanthem exerts a chemotaxis toward eosinophils might, superficially, seem to be a logical explanation for the presence of the primary eosinophilia, how can it explain the reappearance

3. Naegeli, quoted by Bix.[4]

4. Bix, H.: Hämatologische Studien bei Scharlach, Med. Klin. **21**:1689 (Nov. 6); 1728 (Nov. 13) 1925.

of the eosinophilia more than two weeks after the rash has disappeared? I wish to propose tentatively a theory which apparently has not been given any consideration previously but which seems to conform most closely with the data thus far obtained. I believe that the eosinophilia in scarlet fever is a manifestation of the formation of antitoxin in the body during the course of the disease. The primary rise begins to be evident when the condition of the patient is obviously ameliorated, in other words, when sufficient antitoxin has been formed to combat successfully the toxin of the organism of scarlet fever. The free antitoxin in the blood exerts a chemotaxis for eosinophils, thus producing eosino-

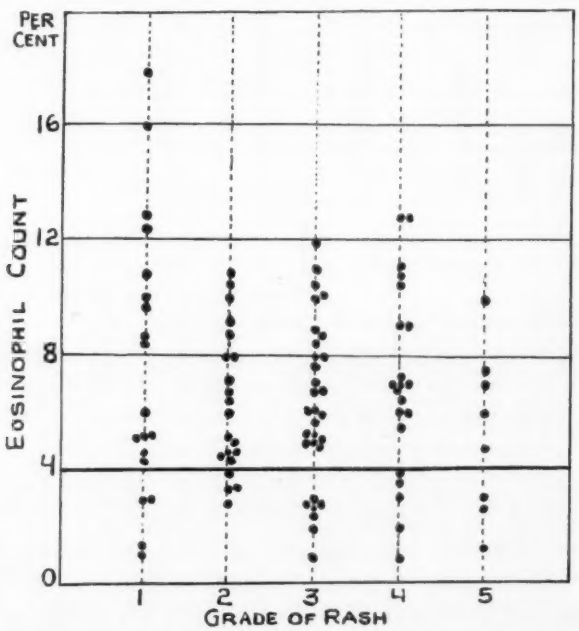

Chart 5.—A comparison of the intensity of the rash and the maximal eosinophil count.

TABLE 3.—*Comparison of the Maximal Eosinophil Count and the Degree of the Exanthem*

Eosinophil Count	Grade of Rash									
	1		2		3		4		5	
	No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent
Over 16 per cent	1	5.3	0	0	0	0	0	0	0	0
12.1 to 16 per cent	3	15.7	0	0	0	0	2	9.5	0	0
8.1 to 12 per cent	5	26.3	5	23.8	8	25.8	5	23.8	1	12.5
4.1 to 8 per cent	6	31.6	12	57.1	16	51.6	9	42.9	4	50.0
Under 4 per cent	4	21.1	4	19.1	7	22.6	5	23.8	3	37.5

philia in the circulating blood. The amount of free antitoxin at this stage of the disease is admittedly slight, and with no further increase in the formation of antitoxin the eosinophilia subsides, but the onset of marked formation of antitoxin toward the end of the third week of illness, a phenomenon which is generally accepted, again provides a marked stimulus which results in secondary eosinophilia. If the eosinophilia is related or attributable to the formation of antitoxin and the presence of free antitoxin in the blood, one would expect eosinophilia to accompany the process of active immunization against scarlet fever. Fortunately, Vaughan [5] has investigated this problem and has found that there is an elevation of the eosinophil count during active immunization against scarlet fever.

SUMMARY

The course of the eosinophil count in eighty-five cases of scarlet fever has been traced and the presence of primary and secondary eosinophilia has been demonstrated. The nature of the phenomenon has been discussed and the view has been expressed that the formation of antitoxin and the presence of free antitoxin in the blood constitute the most logical explanation of the eosinophilia.

5. Vaughan, S. L.: Leukocyte Response in Man to Dick Toxin with Special Reference to Eosinophile Changes, J. Infect. Dis. **50**:315 (April) 1932.

Case Reports

TORSION DYSTONIA AND SO-CALLED BREAST MILK INTOXICATION

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So-called breast milk intoxication, as was reported in a previous article,[1] afflicts only infants about 7 months old (infantile beriberi being seen only in infants about 2 months old), who are nourished with breast milk of the mother or a wetnurse, and the breast milk is considered to be the cause of this illness. The symptoms will not be repeated here in detail, but I wish to emphasize that so-called breast milk intoxication is really encephalitis haemorrhagica superior (or inferior) acuta resulting from breast feeding, as has been proved by anatomic studies. In most instances the patient recovers soon after the breast feedings are discontinued. However, if the infant continues to receive the breast milk, other symptoms will appear in addition to the usual symptoms of so-called breast milk intoxication—motions like those associated with chorea minor and athetosis or other curious movements. These symptoms were present in 25 per cent of my series of twenty-five cases.

ATHETOID, CHOREIC AND OTHER CURIOUS MOTIONS

The peculiar movements which are seen in some cases of so-called breast milk intoxication have been difficult to describe, as no one has pointed out that they represent the symptom complex of torsion dystonia. Heretofore, authors have described the symptoms in various ways, for example, Karasawa[2] wrote: "the baby becomes irritated and picks at the bedclothes. . . . The baby seems to have lost its eyesight and moves its hands recklessly." Inaba[3] said that the patient "involuntarily makes motions with both hands like those seen in cases of chorea." Wakushima[4] reported that in one of his cases there were an "apathetic facial expression, meaningless motions and a low voice . . . the

From the Yamaguchi Red Cross Hospital.

1. Tanaka, T.: So-Called Breast Milk Intoxication, Am. J. Dis. Child. **47**: 1286, 1934.
2. Karasawa, M.: Zika-Zasshi no. 195, 1916.
3. Inaba, I.: Zika-Zasshi no. 210, 1917.
4. Wakushima, M.: Zika-Zasshi no. 224, 1919.

upper limbs make slow and involuntary motions and seldom actually succeed in touching a toy which is proffered. Sometimes the infant grasps the toy, but he soon drops it involuntarily. Often the infant passes the hands over the face or pulls at its clothes." And in another case: "it brings its hand incessantly to the mouth or before the eyes, shutting or opening the palm, or it makes motions as though washing the face with the palm or other various motions." Goto [5] described this curious motion as follows: "Often moving the hand involuntarily." Ito [6] described it in several ways: "Involuntary movement of all the limbs" or "fluttering the arms and legs" or "a motion like that in cases of chorea or athetosis."

These movements resemble those seen in cases of chorea but are much slower; however, they are quicker than those characteristic of athetosis. Many authors have described this symptom as a "motion like that in chorea or athetosis." All agree that it is entirely absent when the infant is asleep and becomes conspicuous when it is irritated, touched or moved. Whether or not this movement is entirely involuntary has been entirely unknown up to now, because the infants with so-called breast milk intoxication are always very young and, moreover, the consciousness is considerably disturbed. In one case, which was observed in the summer of 1933, involuntary choreic movements were found to interfere with voluntary movements but the infant finally attained its aim.

In serious cases of so-called breast milk intoxication either active or passive choreic or athetoid movements of all four limbs are observed. For that reason a voluntary single movement is always disturbed. For example, when the infant wishes to grasp a toy and bring it to the mouth, all the limbs show choreic or athetoid movements and the face also, which is usually apathetic, is distorted by a grimace, that is to say, a voluntary movement accompanies with associated or mass movements.

In such cases, when the physician tries to help the patient who is lying on his back assume a sitting position, a strong opposition to that action results in a pronounced opisthotonos. The trunk and lower limbs become increasingly stiff and bowed, and if the physician places his hands in the nape of the child's neck and attempts to lift the head the child will assume a standing position with the entire body supported by the heels and the neck. However, if one succeeds in making the child assume a sitting position, the tonus of the muscles of the whole body becomes suddenly relaxed. The child cannot remain sitting up but slips and falls forward. If he is then placed on his back, the

5. Goto, M.: Rinsho-Igaku, vol. 6, no. 9, 1918.

6. Ito, S.: Zika-Zasshi, no. 231, 1919.

increased muscle tonus again becomes suddenly relaxed. In the first case, which was reported in 1924,[7] the child made circular movements on the bed as a result of opisthotonos and torsion of the trunk and threw himself almost out of bed.

It is clear that the choreic or athetoid movements interfere with purposeful voluntary movements. In my recent case I could observe a disturbance of tonus in antagonistic and cooperative muscles, as did Oppenheim,[8] Bernstein,[9] Klimenko,[10] Mendel[11] and Araki[12] in their cases. Excessive extension or flexion of the joints consequently occurs and explains why choreic or athetoid movements and torsion dystonia develop. These movements decrease or stop when the infant is quiet or asleep and increase when he is irritated. When he grasps a toy, the hand cannot move directly to the object but proceeds in a roundabout way, accompanied by overflexion and overextension of the fingers and torsion dystonia of the arm, as in cases of athetosis but stronger. When a toy is brought to the mouth, choreic or athetoid movements of all four limbs are again produced. For example, to reach to the mouth the hand goes to the head, comes down as though washing the face and then wanders about the nose. Finally, the toy drops out of the mouth involuntarily. Meanwhile, the other hand makes somewhat similar movements. Sometimes this hand involuntarily pushes the toy away, but the infant does not seem to mind and soon forgets the toy as its will power and memory are weak. If the child sits up, the head and legs waver unsteadily and it soon tumbles down on the floor and then moves both upper limbs as if trying to swim. For the most part the choreic or athetoid movements appear simultaneously in all the limbs; occasionally the tongue (one case) or the right upper limb (one case) shows solitary movements.

REPORT OF A CASE

History.—K. T., a boy 1 year of age, was admitted to the pediatric clinic on Sept. 6, 1933. He was a full term infant and was breast fed. He had learned to crawl and sit up before the present illness had become manifest. He had had no other disease except varicella in May.

The boy had been dull and out of humor since the end of July. His muscles had gradually become weak and he could no longer sit up. On August 4 both eyeballs were observed to be pulled upward for thirty minutes. During the following week convulsive attacks involving the whole body were noted once or twice a day. The child was examined by several physicians, but no abnormality

7. Tanaka, T.: Zika-Zasshi nos. 285, 286 and 287, 1924.
8. Oppenheim, H.: Neurol. Zentralbl. **30**:1090, 1911.
9. Bernstein, S.: Wien. klin. Wchnschr. **25**:1567, 1912.
10. Klimenko, cited by Mendel.[11]
11. Mendel, K.: Monatschr. f. Psychiat. u. Neurol. **46**:309, 1919.
12. Araki, S.: Tokio-Igakukkai-Zasshi vol. 38, p. 1197.

was found. After August 25 the child never cried or made any sound. He was constipated but did not vomit or have fever.

Examination.—The circumference of the head was 43 cm.; the circumference of the chest, 43 cm., and the height, 74 cm. He appeared to be healthy and well nourished. The bone structure and muscle development were good. His attitude was passive and his expresion was lost, apathetic and masked. Movement of the eyeballs was sluggish in all directions. The blinking reflex had been completely lost. The tongue and throat were normal. The skin was pale and tender. His limbs continuously made aimless choreic or athetoid movements; sometimes he seemed to be trying to wash his face with both hands, and sometimes he would flop the lower limbs on the floor. There was no movement when he was sleeping. His head was not firmly supported, and he could not sit up. The patellar reflexes were normal, and the abdominal reflexes were not definite, but the cremasteric reflex was positive. The pupils reacted normally to light. Consciousness was disturbed, the state resembling that of a drunken man. Whether the boy recognized his mother could not be ascertained.

Course.—Lumbar puncture, performed with the child lying on his right side, showed an initial pressure of 160 mm. and an end-pressure of 100 mm. The cerebrospinal fluid was clear. A study of the 3 cc. removed showed no evidence of pleocytosis. The Nonne-Apelt and the Pandy test gave negative results. The sugar content was 0.04 per cent. The boy did not cry while lumbar puncture was being performed without narcosis. When he was sleeping, the knee tendon reflexes could not be elicited and there was no ankle clonus. The Oppenheim and Babinski signs were not present. The cremasteric reflex was not clear because the scrotum was contracted.

On September 7 the child's mother was examined. The dull area of the heart was normal. The pulmonic second sound was slightly increased. There was no paresthesia. Perception of pressure on the calf muscles was increased, particularly on the right side. While the child was lying on the back, he would resist strenuously any attempt that was made to raise his head by placing the hands under the nape of the neck. Such a strong resistance was made that his body became arched like a bow and was finally supported only at the heels and at the nape of the neck. Both the lower limbs were extended and the upper limbs made choreic movements. If one finally succeeded in forcing the child to assume a sitting position, the tonus of the whole body would become suddenly relaxed and the child would soon fall forward on the floor. The boy continually made choreic or athetoid movements when lying on the back. When he looked to one side, horizontal nystagmus developed. The urine was weakly acid and clear and there was a trace of albumin. A few leukocytes were found together with some epithelial cells.

On August 8 the child could change from a supine to a prone position by himself. On August 9 the Wassermann, Sachs and Meinicke tests were negative. On August 12 his color had improved. On August 13 the choreic movements were observed to be decreased. He cried twice for the first time since admission. The cremasteric reflex and abdominal reflexes were positive. On August 18 for the first time the boy cried at injection. He recognized persons at a distance of 0.3 meter.

On August 20 he cried and moaned when pain was inflicted. On August 21 he could hold his head up firmly when in a passive sitting position and he could see persons at a distance of 1 meter. He laughed a little. On August 26 when he cried his voice sounded as it had before he became ill. Paralysis of the left facial nerve could be clearly seen. The liver was palpable 2 fingerbreadths below the

costal margin. The boy seemed to want a toy, so one was given to him. Then the choreic or athetoid movements of the limbs became increased and a curious motion (torsion dystonia) disturbed his grasp of the toy with his right, clawlike hand and he had difficulty in bringing it to his mouth. Soon the choreic movements of the left hand caused the toy to be pushed out of his mouth.

On August 27 examination of the blood (by Dr. M. Okamura) showed: hemoglobin, 78.0 per cent; erythrocytes, 4,766,000; leukocytes, 9,100; color index, 0.81; polymorphonuclears, 55.2 per cent; lymphocytes, 41.2 per cent; mononuclears, 3.6 per cent, and eosinophils, 0.

On August 29 when the patient tried to make any movement, he could not do so because of the strong opisthotonos of the trunk. For example, the harder he tried to suck from a bottle the stronger became the opisthotonos. The choreic or athetoid movements in all the limbs were marked. On September 2 the boy could smile more than before. On September 8 he could be more easily placed in a sitting position. On September 11 the choreic or athetoid movements were remarkably decreased. On September 13 cooperative movements of both hands were still impossible and it was difficult for him to put a toy in his mouth because of an intention tremor of the hand. On September 15 he would grasp a bottle of milk with apparent joy and hunger, but would then seem to forget it when his eye was attracted by anything else. On September 16 the choreic, uneasy movements of the upper limbs were almost negligible, but the flopping movements of the lower limbs had not yet disappeared. He could not sit up but would quickly slip forward. On September 18 the boy responded with a happy voice and expression when his mother greeted him, but his voice did not sound the same as before the illness. He was dismissed from the hospital at the request of the parents.

COMPARISON WITH THE SYMPTOM COMPLEX OF TORSION DYSTONIA

As I have said elsewhere, the choreic or athetoid movements which are characteristic of a patient with so-called breast milk intoxication resemble closely the *eigentümliche tonische Krampfform mit hysterischen Symptomen* which Schwalbe [13] reported in 1908, the movements in the *tonische Torsionsneurose* which Ziehen [14] named and demonstrated in the *Berliner psychiatrischer Versammlung,* the movements observed in the four cases of *Dysbasia lordotica progressiva oder Dystonia musculorum deformans* which Oppenheim [8] reported in 1911, Flatau and Sterling's [15] *progressiver Torsionsspasmus* (1911), those of Mendel's [11] *Torsionsdystonie* and especially those in the case of *Torsionsdystonie* which Budde [16] recently reported.

Torsion dystonia was at first thought to be a distinct disease entity, but lately increasing numbers of cases have been reported in which torsion dystonia is present concurrently with or following other extra-

13. Schwalbe, M. W.: Inaug. Dissert., Berlin, G. Schade, 1908, cited by Mendel.[11]

14. Ziehen, G. T.: Neurol. Zentralbl. **30**:109, 1911.

15. Flatau, E., and Sterling, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:586, 1911.

16. Budde, O.: Monatschr. f. Kinderh. **54**:398, 1932.

pyramidal symptoms, or as an aftermath of encephalitis. Ibrahim [17] is of the opinion that torsion dystonia should be classified either as being symptomatic or as being a separate disease entity. It represents a type of hepatolenticular degeneration and is closely related to the syndrome of double athetosis. As previously stated, so-called breast milk intoxication is encephalitis haemorrhagica superior (or inferior) acuta (C. Wernicke) and the symptom complex of torsion dystonia is seen only in severe cases in which inflammation has spread over the gray matter of the lamina quadrigemina, pons and medulla oblongata.

CONCLUSION

1. The curious choreic or athetoid movements which are often seen in cases of so-called breast milk intoxication in Japanese infants represent the symptom complex of torsion dystonia.

2. Torsion dystonia can be seen not only as a symptom complex but also as a separate disease entity.

17. Ibrahim, J., in Pfaundler, M., and Schlossmann, A.: Handbuch der Kinderheilkunde, ed. 4, Leipzig, F. C. W. Vogel, 1931, vol. 4, p. 356.

OSTEOMYELITIS SUIPESTIFERA

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AND
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B. A., a girl aged 8 months, was admitted to the White Cross Hospital on Nov. 2, 1933, with the complaint of ill health for several weeks, with inability to use the left arm and swelling in the region of the left shoulder. The temperature was 39 C. (102.2 F.).

Examination revealed a well developed child who weighed 7,200 Gm. and was 72 cm. tall. The skin of the face and body was a little pale, the tongue was wet and the lymph glands were normal. The heart and lungs were normal. Neither the liver nor the spleen was palpable. The unique pathologic change was the swelling in the region of the left shoulder. The area was tender on palpation, although passive movements did not seem to cause pain. In the deeper tissues a little fluctuation was observed. The reactions to the tuberculin and Wassermann tests were negative, and the urine was normal. The blood cell count was normal, with 16,800 leukocytes, including 45 per cent segmented cells, 1 per cent eosinophils, 2 per cent monocytes and 52 per cent lymphocytes.

The region of the left shoulder joint was punctured, and 2 cc. of thin, turbid fluid was removed. On examination by one of us (Gajzágó) suipestifer bacilli were isolated. From the fluid drawn on a second puncture, suipestifer bacilli were again isolated.

For identification by culture an agar medium was used, on which a good growth was obtained in twenty-four hours. The homogeneous colonies were small disks about 2 mm. in diameter with smooth sides and were yellow in reflected light and bluish in transmitted light. The organisms were gram-negative bacilli with rounded ends exhibiting vivid motion in a hanging-drop culture. The broth was turbid; gas was developed in dextrose broth, and litmus milk became red and then blue. Milk was not clotted; colorless colonies were grown on fuchsin sulphite agar, and on litmus maltose agar blue colonies were developed. Gas was developed and the colony was greenish yellow on neutral red agar. Indole was not produced in tryptic broth; the Bariekow medium containing dextrose and mannitol was reddened and clotted but no change occurred in the lactose medium. The agglutination test with Bacillus paratyphosus B yielded positive results, but the reaction was stronger with Bacillus suipestifer immune serum. The B. suipestifer immune serum agglutinated the bacterial strain in the highest dilution. On the ground of the identical behavior of the organism with the suipestifer bacillus and related strains the organism was regarded as typical B. suipestifer. This was supported by the agglutination test carried out with the serum of the patient on November 6.

From the Institute of Experimental Pathology of the University of Budapest, director, Prof. S. Belák, and the third medical division of the White Cross Hospital, chief physician, Privatdozent Dr. O. Göttche.

The serum of the patient agglutinated the various suipestifer stocks in dilutions up to 1:2,560 while it agglutinated the other organisms at much lower dilutions or not at all. Repeated examination revealed that the bacilli were not breeding in the blood, the urine or the feces.

It is known that the B. suipestifer may have pathogenicity for man. The number of cases of infection with B. suipestifer reported has increased recently. The infection arises mostly from the eating of contaminated food and causes a condition similar to those seen in patients with typhoid, paratyphoid and dysentery. The most frequent symptom of infection with B. suipestifer is diarrhea, which may be as severe as in dysentery. Similar conditions in infants were observed by Rau.[1]

There was no evidence in the history of previous diarrhea; the parents observed only the swelling in the shoulder region. From October 8 to 22 the infant was in the country with her uncle, who was a gardener on an estate. The child was brought from her uncle's home with the complaint of pain in the shoulder. B. suipestifer was found neither in the feces nor in the urine of the parents, nor did their blood show agglutinins for this organism.

Agglutinations of Various Organisms with the Patients' Serum

Strains	Dilutions of the Serum							
	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	1:5,120
Bacillus suipestifer Berlin	+++	+++	+++	+++	+++	+++	++	—
Bacillus suipestifer Ujpest	+++	+++	+++	+++	+++	+++	+	—
Bacillus suipestifer Manninger	+++	+++	+++	+++	+++	+++	++	—
Bacillus suipestifer, porcine	+++	+++	+++	+++	+++	+++	++	—
Bacillus suipestifer White Cross	+++	+++	+++	+++	+++	+++	++	—
Bacillus Voldagsen	+++	+++	+++	++	++	+	—	—
Type Newport	+	+	+	+	+	—	—	—
Bacillus erzindjan	+	+	+	+	+	—	—	—
Bacillus enteritidis bresl	—	—	—	—	—	—	—	—
Bacillus paratyphosus B	—	—	—	—	—	—	—	—

It was impossible to examine the persons living on the estate. However, the director of the estate informed us that there had been no illness in the last year either among the men or among the animals. The source of infection was therefore doubtful. Because the examination of the parents gave negative results and because there were no domestic animals in the home of the parents we think that the infection must have originated on the estate.

During the patient's stay in the hospital the swelling in the shoulder region increased. The temperature was high. The patient did not give the impression of being very ill, for her appetite was satisfactory and the feces were normal.

Roentgenograms made on admission showed a periosteal thickening at the proximal metaphysis of the left humerus on both sides and a small area of rarefaction on the outer part of the upper end of the left diaphysis. There was evidence of typical osteomyelitis. The shoulder joint seemed to be normal. We cannot say whether the abscess arose in the joint or from the inflamed area about the humerus. The fact that the left shoulder was movable suggested that the joint was healthy. Incision of the abscess made on November 10 by Dr. Szombati threw no light on the question. Among the fibers of the deltoid muscle an abscess cavity was found with from 3 to 4 cc. of pus. No bone deprived of its periosteum was found, and the surgeon was unable to probe the cavity of the joint. Nothing could be concluded from the fact that the cavity of the joint could not be reached. There were no findings to indicate whether the source of the pus was intra-

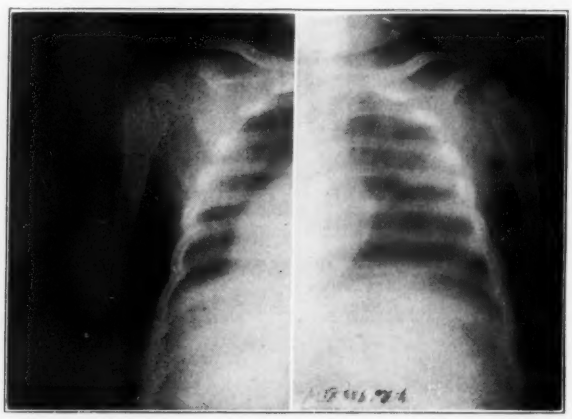
1. Rau, H.: Ztschr. f. Kinderh. **52**:510, 1932.

articular or peri-articular. Because roentgenograms taken later showed destruction of the epiphysis, we assumed that the process extended into the shoulder joint.

According to Paschlau [2] in 41 per cent of cases of infantile osteomyelitis the process extends into the cavity of the joint, especially when the apophysis is involved.

The temperature fell after the abscess was drained, and the course was subfebrile for two weeks, after which the temperature was normal. The wound healed in three weeks, and the swelling went down. The child began to move her left arm. The roentgenogram taken at this time showed continued periosteal thickening and rarefaction of the bone. The lateral kernel of the epiphysis had disappeared.

The child when discharged on December 17 was clinically healthy. The roentgenogram taken on that day showed that the periosteal thickening was unchanged but that the inner kernel of the epiphysis was smaller and the distal edge seemed to be eroded. Thus we concluded that in spite of the clinical recovery the process had gone further and destroyed the epiphysis. Agglutination occurred in a dilution of 1 : 640.



A roentgenogram taken on December 1.

COMMENT

This type of infection with B. suipestifer is rare, although similar infections including complications in the bones and joints have been reported in increasing numbers lately. Bosch [3] in the Netherlands Indies in 1928 saw an infant aged 11 months who had gonitis suppurativa caused by B. suipestifer. In the same place Dijkstra and van der Hoeden [4] in 1929 saw a child aged 1½ years with a purulent infection in the elbow and a child aged 2 years with an infection in the shoulder joint.

2. Paschlau: Monatschr. f. Kinderh. **55**:230, 1933.

3. Bosch, W. G.: Geneesk. tijdschr. v. Nederl.-Indië **69**:42 (Jan. 21) and 462 (May 10) 1929.

4. Dijkstra and van der Hoeden: Nederl. tijdschr. v. geneesk. **1**:1458 (March 23) 1929.

Van Creveld and Ruys [5] in Amsterdam in 1933 observed an infant aged 5 months who had pneumonia; seven weeks later the left knee swelled and B. suipestifer was isolated from the pus. Kuttner and Zepp [6] in 1933 published reports on the interesting cases of four patients in Baltimore: a man who had pyelitis; a child aged 2 years who had first pneumonia and then purpura followed by death; a child aged 19 months, with an infection in the left knee joint, and an infant aged 5 weeks who had osteomyelitis in the proximal metaphysis of the humerus extending into the shoulder joint.

A case similar to the one last mentioned was described by Nabarro, White, Dyke and Scott [7] in London in 1928. They observed an infant 8 months old in whom swelling in both shoulder joints developed without a sign of previous illness. Roentgenograms showed osteomyelitis of both humeri. It is probable that the process extended to the shoulder joints.

In the cases reported in the literature there was infection in the shoulder in two instances (Bosch and Dijkstra and van der Hoeden), in the elbow in one (Dijkstra and van der Hoeden) and in the knee in two (van Creveld and Ruys, and Kuttner and Zepp) and osteomyelitis in the humerus in three instances (cases of Nabarro and his co-workers and Kuttner and Zepp, and our case).

The distinction between osteomyelitis and diseases in the joints is not exact. Without denying the possibility of primary arthritis we believe that in most cases arthritis follows osteomyelitis. This was shown by the research of Paschlau of the Finkelstein school.

According to him diseases in the joints due to the pneumococcus are usually the consequence of osteomyelitis. The localization of osteomyelitis of childhood, according to Paschlau, usually occurs in the proximal metaphysis, and in 41 per cent of cases the process extends into the joint. If the process spreads, as it may do early, the inflammation of the joint covers the small kernel of the bone. For this reason one never knows whether the process originates in the bone. In our case and in the cases of Kuttner and Nabarro and his associates the osteomyelitic process extended into the joint. Paschlau recommended the term osteomyelitic arthritis in such cases.

The reports of the eight cases published are interesting because there was no history of previous illness except in the case reported by van Creveld and Ruys. Even the usual diarrhea was absent. The first manifestation of infection was suppuration of the bones or of the joints.

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5. van Creveld and Ruys: Ztschr. f. Kinderh. **54**:725, 1933.

6. Kuttner, A. G., and Zepp, H. D.: Salmonella Suipestifer Infections in Man, J. A. M. A. **101**:269 (July 22) 1933.

7. Nabarro, White, Dyke and Scott: Lancet **2**:868, 1929.

It is difficult to determine how long after the infection sets in inflammation of the bones and joints occurs. In the case reported by van Creveld and Ruys there was a latent period of seven weeks following pneumonia, but it is not known whether the pneumonia was caused by B. suipestifer.

Inflammation of the bones and joints following infection with any strain of B. paratyphosus may arise during the course of the primary infection or within two months after it, or it may remain latent for years (Hesse,[8] Ssokoloff [9]). Because of the close relation between the paratyphoid bacilli and B. suipestifer one may assume that the complications arise at the same time.

The source of infection is in most cases unknown. In the case of van Creveld and Ruys five pigs in the house in which the child lived died of an unknown disease. In our case there was propinquity to pigs, but in the reports of the other cases no mention was made of pigs. Infection through food cannot play a large part in cases in infants and children! In Kuttner's case the patient was an infant aged 5 weeks who received only mother's milk, and our patient received boiled milk, cream of wheat, soup and vegetables. Persons with whom the children came in contact were clinically and serologically healthy, except the mother of one of Kuttner's patients, whose serum showed agglutination for B. suipestifer.

It is interesting to us that such complications in the joints and bones are found only in infants and children. Age probably plays a rôle. It is well known that in various infections of childhood metastases occur to the joints and bones, for example, a pneumococcic infection after a disease process in the lungs.

The aforementioned cases are alike in that the infections were very mild. In each case the author agreed that the patient did not give the impression of being very ill. The process healed within from two to three months in each case. This is not unusual in osteomyelitis of childhood.

In most cases in childhood the inflammation is localized in the metaphysis, the periosteum is raised, and the process extends into the soft parts or the joints. This inflammation of the joints is not like that seen in later years, because there is prompt recovery. This seems to be a characteristic of childhood rather than the result of infection by different bacilli. One often observes the same process in infections with streptococci, pneumococci and influenza and colon bacilli, though not in all cases. There are other kinds of infection which cause severe illness which may end fatally within two or three days.

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8. Hesse: Arch. f. klin. Chir. **128**:739, 1924.
9. Ssokoloff: Beitr. z. klin. Chir. **133**:321, 1925.

Infection with B. suipestifer is not always mild. We stated earlier that the illness sometimes resembles typhoid, paratyphoid or dysentery, is often very severe and is sometimes fatal. The fact that the disease process in these eight cases was mild in spite of complications in the bones and joints does not signify a great deal, because the material is very limited.

The small number of cases reported moved us to report our case to encourage the further collection of facts on the subject.

PRIMARY STAPHYLOCOCCIC PNEUMONIA

COMPLICATED BY EMPYEMA, SEPTICEMIA, MULTIPLE ABSCESSES AND OSTEOMYELITIS OF THE SKULL AND SECOND METACARPAL BONE OF THE RIGHT HAND, WITH RECOVERY

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AND
DON F. CATHCART, M.D.
ATLANTA, GA.

Owing to the anatomic structure of the lung it is difficult to state that pneumonia is caused by a single organism. The anatomic diagnosis of pneumonia is usually not difficult, but at times the etiologic diagnosis presents difficulties. Reimann stated:[1] "It is of no great moment from the standpoint of specific prophylaxis, therapy or prognosis whether the lesion in pneumonia is in the alveoli or in the interstitial tissue, but it is of great importance whether the infection is due to the pneumococcus, type 1, or the staphylococcus. In other words, etiologic diagnoses must eventually supplant anatomic diagnoses."

The case reported here conforms to the clinical picture of staphylococcic pneumonia, and staphylococci were obtained (1) from the blood stream, (2) from pus withdrawn from the pleural cavity, (3) from pus aspirated from the soft tissues of the hand and scalp and (4) from material obtained by open drainage of the second right metacarpal bone and temporal bone. The cultures were all pure strains, there being no contamination with other organisms.

REPORT OF A CASE

H. C., a Negro boy, 6 years old, was admitted to the Emory University Division of Grady Hospital on Sept. 26, 1933, complaining of cough, fever, pain in the stomach and swelling of the left cheek and right hand. One week prior to admission he suddenly became ill with high fever and pain in the abdomen, in the right side of the chest and in the right arm. He remained in bed, continued to have a high temperature, sweated profusely and had one severe chill. Three days before admission swelling began at the base of the right thumb and between the thumb and the index finger. In twenty-four hours the entire right hand was swollen and tender. A swelling of the right cheek was noted, but this was not painful.

The history included nothing of importance except unilateral specific parotitis at the age of 3 years. The family history was essentially irrelevant.

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1. Reimann, H. A.: Primary Staphylococcic Pneumonia, J. A. M. A. **101:** 514 (Aug. 12) 1933.

The initial examination on admission revealed an acutely ill child, with a temperature of 101.4 F., a respiratory rate of 60 per minute and the pulse rate rapid and weak. There was a nasal discharge, and the throat was inflamed. Respiratory distress was noticeable, and examination of the lungs revealed moderate decrease in the breath sounds in the region of the right axilla and over the upper portion of the right lung posteriorly. A marked decrease in the intensity of the breath sounds and some impairment of resonance were noted over the lower lobe of the right lung posteriorly. The abdomen was normal.

The right cheek was slightly swollen, but there was no tenderness. The right hand was markedly swollen and very painful. The swelling was uniform, and no localized areas of fluctuation were noted.

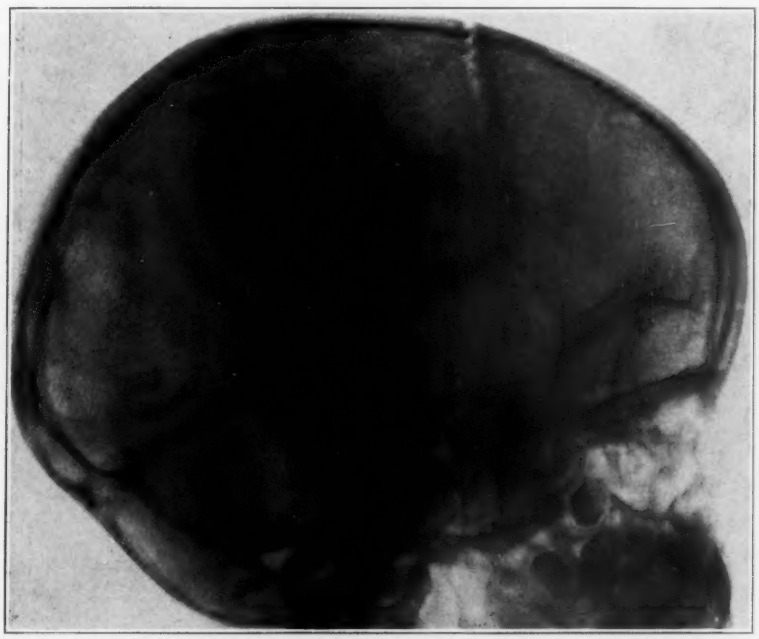

Fig. 1.—The skull, fifteen days after admission, showing no pathologic change in the bone.

Urinalysis on admission showed: albumin, 2 plus; a few pus cells, and fine granular casts. The erythrocyte count was 3,900,000, and hemoglobin was 70 per cent. The leukocyte count was 25,000, with 91 per cent polymorphonuclears. Roentgen examination of the chest revealed: increased density over the lower lobe of the right lung and interlobar pleural thickening, suggestive of a pneumonic lesion. At the same time roentgen examination of the right hand and skull revealed no evidence of diseased bone. A spinal puncture was done; the fluid was clear, was under no pressure, contained 3 cells and showed a negative reaction for globulin. The Wassermann reactions of the spinal fluid and blood were negative.

Four days after admission an abscess developed in the right hand which was incised and drained. Culture of the material revealed a pure strain of small gram-

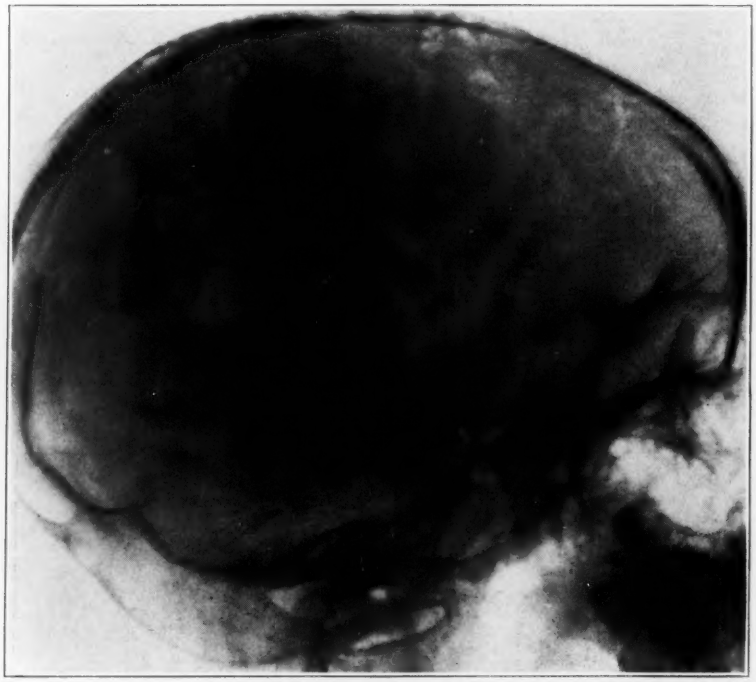

Fig. 2.—The skull, forty-five days after admission, showing extensive osteomyelitis of the skull.

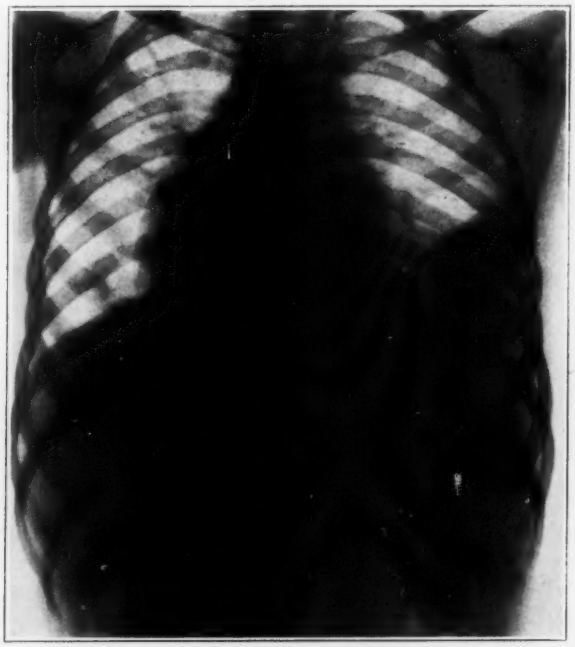

Fig. 3.—The chest, fifteen days after admission, showing fluid in the right pleural cavity.

positive staphylococci. The abscess continued to drain for about ten days and then apparently healed. Two weeks later the hand again became swollen and tender, and a roentgenogram showed a destructive lesion of the second metacarpal bone involving the entire structure. An incision was made over the area, and free pus was obtained.

On the seventh day in the hospital a blood culture was taken. The temperature during the interval was septic, and the child's clinical symptoms were those of septicemia. The culture proved positive and a pure strain of gram-positive staphylococci was recovered. Blood cultures taken one week and one month later were negative.

Fig. 4.—The chest, forty-three days after admission, showing no evidence of fluid in the right pleural cavity.

A septic temperature continued and on the ninth day in the hospital there developed a swelling over the left parietal region. Fluctuation developed two days later, and thick, yellow pus was aspirated from the area. The abscess was then incised and drained freely. Staining and culture of the material revealed gram-positive staphylococci. A roentgenogram of the skull revealed no evidence of a pathologic change in the bone. The abscess drained profusely for a few days, after which the discharge became pale and watery. This continued until the child left the hospital. Ten days prior to discharge from the hospital a roentgenogram of the skull showed typical destructive lesions of osteomyelitis.

During the first two weeks of hospitalization repeated examinations of the chest revealed little more than was found on admission. There was no tendency toward resolution, and the observations suggested pneumonia. On the fifteenth day after admission percussion revealed a small area of flatness at the base of the

right lung, and a roentgenogram confirmed the diagnosis of a small effusion. Two days later thoracentesis yielded 42 cc. of thick, creamy pus. The material showed gram-positive staphylococci on staining and culture. One week later a roentgen examination revealed a marked increase in the density and extent of the shadow at the base of the right lung. Thoracentesis was repeated, and 34 cc. of thick, gray pus was obtained. A few days later a third thoracentesis was done, and 30 cc. of thick pus was obtained. From this time the signs in the right side of the chest became less evident, and the lung began to function more normally. A roentgenogram taken one month after admission showed a markedly thickened pleura and a small encapsulated pocket of air at the base of the right lung.

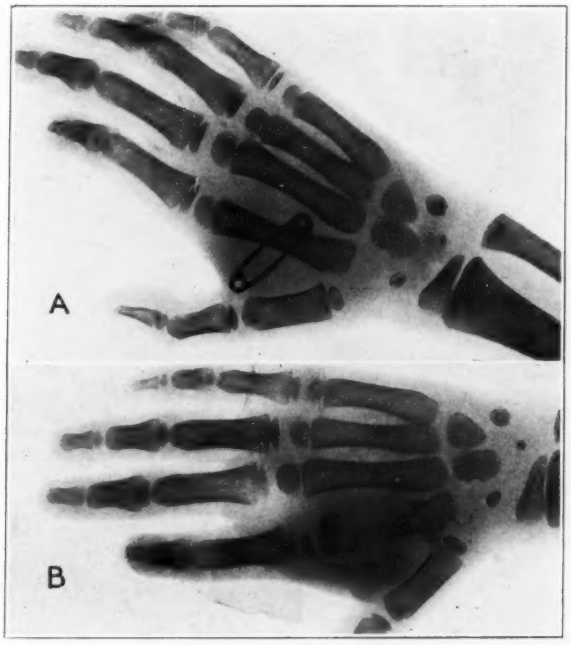

Fig. 5.—*A*, the right hand, ten days after admission, showing no evidence of pathologic change in the bone; *B*, the right hand, thirty days after admission, showing a destructive lesion of the second metacarpal bone.

At the end of one month the child's temperature began to drop gradually toward normal, but it remained septic. The leukocyte count was 15,200, with 83 per cent polymorphonuclears. A tuberculin test gave negative results.

On several occasions during the most critical period of the illness, transfusion was done. The condition gradually became better, the signs in the chest cleared up, and a roentgenogram of the chest on November 21, almost two months after admission, showed no evidence of empyema but showed a thickened pleura and some bronchial thickening in the lower lobe of the right lung. A few days before dismissal a final blood count showed: erythrocytes, 3,000,000; hemoglobin, 60 per cent, and leukocytes, 12,400, with 64 per cent polymorphonuclears.

When the patient was dismissed from the hospital, on November 24, there was still a thin discharge from the incisions on the scalp and in the right hand. He was instructed to report to the surgical outpatient department for further observation. He was seen on Feb. 7, 1934, at which time the temperature was normal and there was no drainage from either wound. Excessive granulation tissue at the site of the incision on the hand was treated with fused silver nitrate.

Progress in Pediatrics

MENINGOCOCCIC AND NONMENINGOCOCCIC MENINGITIS IN THE NEW-BORN AND IN YOUNG INFANTS

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There is no disease, with the exception of diphtheria, in which the early detection and determination of the correct etiologic diagnosis is of such prime life-saving importance as in meningococcic meningitis. Any additions to the literature on this subject which emphasize this fact and furnish data that may be helpful in making physicians more keenly aware of the early diagnostic characteristics of meningitis should be of great value for the public health. In infants meningitis, of whatever etiology, is frequently indefinite, atypical, protean and masked in its clinical manifestations—a fact which explains the usual delay in diagnosis and treatment and the consequent extremely high mortality rate. Meningococcic meningitis in infants under 1 year of age is relatively rare and in the new-born and in infants in the first weeks and months of life it is still rarer. The cases presented here were in the new-born and in young infants and showed the characteristic atypical clinical manifestations of meningitis at that age. Because of these facts, it is deemed worth while to report these cases as illustrative of the special features of meningitis in the first months of life and thus bring the whole subject to the forefront. As nonmeningococcic meningitis in patients of this age differs little in its clinical aspects from meningococcic meningitis, and as it presents especially interesting pathogenic aspects, it will be included together with illustrative cases in this general review.

REPORT OF CASES

CASE 1.—This case, because of the early age at which it occurred and the unusual manifestations which developed, formed the basis and stimulated the writing of this article.

E. N., a white boy aged 27 days, was admitted to the New York Post-Graduate Medical School and Hospital on Jan. 7, 1929, because of abdominal cramps, constipation and persistent crying for two days. On examination he was found to be well developed and well nourished. He cried intermittently, especially when the

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abdomen was touched. The epigastrium was bulging. The abdomen, however, was soft and apparently normal. Except for an occasional twitching of the extremities, the examination revealed no abnormalities. The temperature was 98.8 F.; the pulse rate, 120, and the respiratory rate, 36. The blood count showed 19,900 leukocytes with 71 per cent polymorphonuclears. The tentative diagnosis on admission was intussusception, pyloric stenosis and obstruction.

Soon after admission the temperature rose from 101 to 102 F. The infant had been crying incessantly and had been in the habit of drawing up the knees. The possibility of meningitis suggested itself. Spinal puncture was performed; the fluid was scant and its culture remained sterile after twenty-four hours' incubation. On the third day twitching of the extremities and later bulging of the fontanel were noted. Spinal and ventricular punctures were unsatisfactory. Cisternal puncture yielded cloudy fluid containing intracellular gram-negative diplococci, which were identified later as meningococci. Antimeningococcus serum was then given for eight days. The infant died on the eighth day after admission.

At postmortem examination performed two hours after death I found evidence of a widespread fibrinopurulent pia-arachnitis involving the convexity as well as the base of the brain with a localized area of extension to the cerebral cortex in the frontal lobe and early internal hydrocephalus. Both the gross and the microscopic picture in no way differed from those in meningitis in older children and adults. There were also patchy bronchopneumonia and cloudy swelling of the viscera.

Case 2.—G. K., a white girl aged 2 months, was admitted to the New York Post-Graduate Medical School and Hospital with the history of high fever, diarrhea and abdominal cramps of ten days' duration. On the day prior to admission the infant became drowsy and irritable and cried whenever she was awakened. It was reported that there had been "a few petechiae over the chest." The fontanel was slightly bulging, and the Brudzinski and Kernig signs were present. The infant was extremely irritable and cried incessantly. Spinal puncture yielded fluid which showed an abundance of tinctorially and later culturally identified meningococci. Antimeningococcus serum was administered on the day of admission and for eight consecutive days in doses of 20 cc. per day. Gradual improvement resulted, and the infant was discharged as cured on the seventeenth day after admission. The prominence of the gastro-intestinal symptoms in this case is of great interest.

Case 3.—R. C., a white boy aged 18 days, was admitted to the New York Post-Graduate Medical School and Hospital with the history of abdominal cramps of two days' duration. A high fever developed, and he did not nurse well. On admission he was moribund, and there was bulging of the fontanel. The Brudzinski sign was present, but no other signs were noted. Spinal puncture was immediately performed and antimeningococcus serum administered. Ten minutes after admission the infant died. Postmortem examination revealed evidence of purulent mastoiditis and septic meningitis, with Streptococcus haemolyticus as the infecting organism. The symptoms and signs in this case also for two days prior to admission had pointed to involvement of the gastro-intestinal tract rather than to that of the central nervous system.

Case 4.—R. S., a white boy 3 months of age, was admitted to the New York Post-Graduate Medical School and Hospital with a history of high fever and listlessness of one day's duration.

On examination the infant was found to be well developed and well nourished. He was drowsy but could be easily aroused and would cry vigorously. The pharynx was slightly injected, and the cervical lymph nodes were enlarged. The

right tympanum was bulging. The Kernig sign was only suggestive, but the Brudzinski sign was definite. The temperature was 101 F.; the pulse rate, 150, and the respiratory rate, 50. Spinal puncture yielded a cloudy fluid containing 760 leukocytes with 53 per cent polymorphonuclears. Antimeningococcus serum was immediately administered. Culture of the spinal fluid later showed the presence of pneumococcus type IV. Paracentesis of the ear drums yielded pus. Ethylhydrocupreine hydrochloride was given intrathecally. The infant died five days after admission. On postmortem examination there were evidences of purulent meningitis and purulent otitis media and cloudy swelling of the viscera. It is noteworthy that even two days after admission and with the diagnosis of meningitis well established the meningeal signs were scant. Incessant crying was the outstanding symptom here as well as in the 3 preceding cases.

CASE 5.—W. L., a white boy 5 months of age, was admitted to the New York Post-Graduate Medical School and Hospital with the history of fever, drowsiness and refusal of feeding for one day. Examination showed that he was well developed and well nourished, but he looked sick and cried incessantly. The temperature was 101.5 F.; the pulse rate, 125, and the respiratory rate, 28. The fontanel was tense. The abdomen was spastic. Neurologic examination revealed no abnormality. A tentative diagnosis of gastro-enteritis and possible appendicitis was made. For two days no additional signs or symptoms were noted. On the third day the fontanel was bulging, the neck was retracted and the Kernig sign was present. A spinal tap was then performed and yielded a cloudy fluid with tinctorially recognizable meningococci. Antimeningococcic serum was immediately given. After only four daily injections of serum the signs and symptoms cleared up, and recovery was complete by the tenth day after admission.

CASE 6.—J. J., a white boy aged 4 weeks, had "twitchings of the body" for three days. On admission to the Israel Zion Hospital he showed intermittent facial spasms and twitching of the upper and lower extremities. Breathing was stridulous. He had been crying loudly. No other signs were elicited. The temperature was 100 F. The blood calcium value was 7.2 mg. and the phosphorus 3.2 mg. per hundred cubic centimeters. A tentative diagnosis of intracranial hemorrhage or tetany was made. Spinal puncture was attempted on two occasions but was unsuccessful. Cisternal puncture was then performed and yielded a cloudy fluid with 1,200 white cells per cubic millimeter with polymorphonuclears predominating. A smear showed no bacteria. Antimeningococcus serum was then injected. Cisternal punctures were made daily for seven successive days and once a ventricular puncture also was made. Culture of the fluid at first yielded B. coli and later also streptococcus. The patient's condition improved somewhat and the convulsions disappeared entirely. There was only a slight rigidity of the neck, no other signs being present. A blood culture yielded Streptococcus haemolyticus. On the sixteenth day after admission signs of pneumonia appeared and ptosis of the right eyelid and nystagmus developed. Spasticity gave place to atony. The infant grew weaker, the temperature rose to 103 F. and on the seventeenth day he died. At postmortem examination there was found a diffuse, purulent pia-arachnitis of the brain and cord with early internal hydrocephalus, also a patchy bronchopneumonia, pyelitis and focal nephritis.

INCIDENCE AND FREQUENCY

Meningitis in the new-born and during the first few months of life has always been considered so rare that reports of single cases have

appeared in the old as well as in the recent literature. Boirivant [1] collected reports of 34 such cases from the literature for the period from 1891 to 1908. Barron,[2] in a careful review of the literature in 1918, collected reports of only 42 cases in the new-born and in early infancy. In only 5 of these cases was the meningococcus the infecting organism, the remaining cases having been caused by several different organisms, with Bacillus coli predominating. Koplik [3] observed meningitis in 12 infants less than 3 months of age between the years 1909 and 1916, and of these cases 4 were due to the meningococcus. In a statistical study of 272 cases of meningitis at the children's clinic at Nancy between the years 1895 to 1913 Haushalter and Remy [4] found that the youngest patient with meningococcic meningitis was 2 months old. Root [5] in 1921 found reports of only 6 cases of meningococcic meningitis in infants less than 2 months of age, and only 1 of the patients had obstructing hydrocephalus. Cooke and Bell,[6] reviewing the literature on meningococcic meningitis in infants of that age, found reports of only 12 cases within the five year period from 1917 to 1922. In their 35 consecutive cases of meningococcic meningitis in infants less than 2 years of age at the St. Louis Children's Hospital, 4 patients were under 3 months. Sturtevant [7] in 1926 said that he considered meningococcic meningitis to be so rare in early infancy that he reported 1 case in a 7 week old infant who recovered from the disease. Karplus [8] in 1927 collected reports of 37 cases of meningitis in infants, of which only 4 were caused by the meningococcus. During a period of eight years, among 50 infants with meningococcic meningitis who were treated at the Karolinen Kinderspital in Vienna, Karplus found only 1 case, her own, in an infant less than 2 months of age. Borovsky [9] reported in 1930, that of 190 patients with meningococcic meningitis admitted to the Cook County Hospital in Chicago within a period of eighteen months, the youngest was 3 months old. In McLean and Caffey's [10] series, of

1. Boirivant, Anna: La méningite chez les nouveau-nés, Thèse de Paris, no. 215, 1908.

2. Barron, M.: Am. J. M. Sc. **156**:358 (Sept.) 1918.

3. Koplik, Henry: Arch. Pediat. **33**:481 (Oct.) 1916.

4. Haushalter and Remy, A.: Rev. méd. de l'est **45**:533 (Oct.) 1913.

5. Root, J. H.: A Case of Meningococcus Meningitis with Obstructive Hydrocephalus in the Newly Born, Am. J. Dis. Child. **21**:500 (May) 1921.

6. Cooke, J. V., and Bell, H. H.: The Incidence of Meningitis in Early Infancy: With a Description of Two Cases Due to Unusual Organisms, Am. J. Dis. Child. **24**:387 (Nov.) 1922.

7. Sturtevant, James M.: Meningococcus Meningitis with Recovery in Seven Weeks Old Infant, J. A. M. A. **86**:1436 (May 8) 1926.

8. Karplus, Dora: Wien. klin. Wchnschr. **40**:250 (Feb. 24) 1927.

9. Borovsky, Maxwell P.: Am. J. M. Sc. **179**:82 (Jan.) 1930.

10. McLean, Stafford, and Caffey, John P.: Endemic Meningococcus Meningitis, Am. J. Dis. Child. **35**:357 (March) 1928.

136 infants with endemic meningococcic meningitis the youngest was 23 days old. Even as recently as 1933 Brown and Silverthorne [11] presented a report of a single case of meningococcic meningitis in a 22 day old infant with complete recovery.

To gain an idea as to the average frequency, age incidence and distribution of all cases of meningitis in early infancy in a representative hospital of a metropolitan area, a statistical study was made of the patients that came under observation at the New York Post-Graduate Medical School and Hospital for the period of four years, from 1928 to 1931, inclusive.

Incidence of Meningitis in Relation to Age and Etiology in the Babies' Ward of the New York Post-Graduate Hospital During the Four Year Period 1928 to 1931

	Year				
Number of patients	1928	1929	1930	1931	Totals
Three months of age or younger					
Meningococcic meningitis	1	2	0	0	3
Nonmeningococcic meningitis	0	1	1	3	5
Three months to one year of age					
Meningococcic meningitis	4	2	9	4	19
Nonmeningococcic meningitis	3	1	4	5	13
Over one year of age					
Meningococcic meningitis	40	25	0	3	68
Nonmeningococcic meningitis	7	3	1	2	13
Total number of patients with					
Meningococcic meningitis	45	29	9	7	90
Nonmeningococcic meningitis	10	5	6	10	31
Meningitis	55	34	15	17	121
Total number of patients admitted to the pediatric department	1,812	1,385	1,495	1,470	6,162
Percentage of patients with					
Meningitis	3.03	2.44	1.00	1.15	1.96
Meningococcic meningitis	2.42	2.1	0.6	0.47	1.46
Percentage of patients 3 months of age or younger					
With meningitis	1.82	8.81	6.67	17.64	6.6
With meningococcic meningitis	1.82	5.88	0	0	2.48
With nonmeningococcic meningitis	0	2.94	6.67	17.64	4.13
Percentage of patients 3 months to 1 year of age	12.72	8.81	86.67	52.94	26.44
Percentage of patients over 1 year of age	85.54	82.35	6.67	29.94	66.94
Percentage of patients with meningococcic meningitis 3 months of age or younger	2.22	6.89	0	0	3.33

From the accompanying table it can be seen that of the total number of 6,162 children admitted to the babies' ward of the New York Post-Graduate Medical School and Hospital, 121 (1.96 per cent) had meningitis, only 3 of the patients with meningococcic meningitis and only 5 (2.5 per cent of the 121) of those with meningitis due to other organisms (4.1 per cent of the 121) were infants under 3 months of age.

The foregoing, brief review of the literature shows that almost all reviews on the subject—the present one not being excluded—lack in thoroughness as far as the collecting of all instances in the literature is

11. Brown, A., and Silverthorne, Nelles: Meningococcic Meningitis in Infancy: Report of a Case, J. A. M. A. **101**:272 (July 22) 1933.

concerned. Furthermore, as many cases are probably never reported and a still greater number are not correctly diagnosed and are missed altogether, it therefore seems that an exhaustive study of this subject is of somewhat doubtful value. At the same time it is clearly evident from the foregoing review that in the first two or three months of life meningitis, especially the meningococcic variety, though not as rare as is commonly believed, is nevertheless relatively rare and therefore merits special study.

CLINICAL PICTURE

It is not generally recognized that meningitis in the new-born and in young infants differs considerably in its clinical features from that in older infants and children. Alfred Stillé,[12] in his classic treatise on "Epidemic Meningitis" in 1867, twenty years before the discovery of the correct etiology of the disease by Weichselbaum, called it "a chameleon-like disorder." This apt simile and his remark that "no single typical case, nor any general description, can accurately represent this Protean affection, as a whole, nor convey a just idea of its numerous grades and multiform aspects," are especially true of meningitis in the new-born and in young infants, for it is the masked and atypical form that is common at that age. The classic signs of meningitis, such as rigidity of the neck and the Kernig, Brudzinski and other signs, are at the beginning usually prominent by their absence. It is only when the disease is moderately advanced that some of these signs may be elicited. This is true of both the endemic and the epidemic form of the disease as well as of the other types of septic "primary" meningitis that are caused by organisms other than the meningococcus. Thus, at the Babies' Hospital in St. Louis, according to McLean and Caffey,[10] meningitis was not recognized in 136 infants prior to their admission to the hospital and in some cases the diagnosis was not reached even after many days in the hospital.[13]

Although no special symptom complex or definite set of pathognomonic signs of meningitis is found at this age, there are nevertheless some signs and symptoms which, when the proper attention is focused on them, may suggest the presence of meningitis.

Onset.—Though in many cases the onset may be sudden, it is usually gradual and insidious and may exhibit delusive features which turn the attention of the clinician away from the central nervous system.

General Appearance.—In the initial stages the infant may present the following features: loss of vivacity, somnolence or fretfulness,

12. Stillé, Alfred: Epidemic Meningitis or Cerebro-Spinal Meningitis, Philadelphia, Lindsay & Blakiston, 1867, pp. 22 and 178.

13. It may be added that occasionally the diagnosis of meningitis is missed in older children or even in adults.

restlessness, irritability, hyperesthesia and excessive responsiveness to external stimuli. There is also usually refusal to nurse. Hyperesthesia may dominate the entire picture. Crying, the incessant, desperate or groaning type, which is spontaneous or which is brought about by the slightest touch as though pain were evoked, seems to be the most prevalent single symptom.

Nutrition.—This is rapidly impaired and often is the chief difficulty, at times being the only objective finding. Because of this a diagnosis of congenital debility is often made and meningitis is discovered only on postmortem examination.[14]

Skin.—Eruptions are rather unusual in early infancy. However, cases have been reported in which there were petechial, macular, papular or bullous rashes that were either localized or diffuse.

Eyes.—Purulent conjunctivitis may be the first sign to usher in meningitis, but it is usually diagnosed at first as being of gonococcic origin, the true aspect of the disease manifesting itself only several days afterward.[15] The reverse, namely, the mistaking of gonococcic for meningococcic conjunctivitis, also may occur.

Gastro-Intestinal Symptoms.—Meningitis in early infancy is practically always ushered in by a gastro-intestinal disturbance of some sort. This may take the form of abdominal cramps and mild diarrhea without any special characteristics. Vomiting is not as constant a feature as in older children, occurring in from 50 to 60 per cent of cases.[16] It is nonprojectile, being more in the form of regurgitation, has no relation to the feeding and in general cannot be differentiated from vomiting caused by other afflictions in early infancy. The gastro-intestinal symptoms may be the only ones present, so that a diagnosis of acute gastro-enteritis is commonly made. These symptoms usually appear without any demonstrable cause and do not respond to the accepted methods of treatment.

Temperature and Pulse and Respiratory Rates.—In the initial stage the temperature may be about normal or may show a slight rise, while the pulse and respiratory rates may increase considerably. Later, the temperature also rises but the curve is irregular and shows no special characteristics. Even then the pulse rate and at times also the respiratory rate are increased out of proportion to the rise in temperature. This dissociation between the pulse rate and the temperature, in the

14. Scheib, Alexander: Prag. med. Wchnschr. **5**:169, 1900.

15. White, T. W.: Arch. Pediat. **34**:372 (July) 1917. Miller, D. J. M.: ibid. **34**:824 (Nov.) 1917.

16. (*a*) Cantalamessa, Vittorio: Pediatria **39**:233 (March 1) 1931. (*b*) Neal, J. B., and Jackson, H. W.: Epidemic Meningitis in the First Three Months of Life, J. A. M. A. **88**:1299 (April 23) 1927.

opinion of many observers, is an important diagnostic sign of meningitis in early infancy.

Signs in the Head and Neurologic Signs.—Tension or bulging of the fontanel, according to most observers, is practically always present and is one of the most reliable signs of meningitis in early infancy. However, it may be present also in pneumonia, acute otitis media and other infections of infancy.

Reflexes.—Normal or pathologic reflexes are unreliable and of little value at this age. The Kernig sign is usually slight or doubtful and often cannot be elicited even in a clearcut case until a later period. The Brudzinski sign is difficult to obtain. Rigidity of the neck may be slight or absent. Muscular tremors or twitchings may occur, which are sometimes mild, resembling chills, and sometimes severe. They also, however, may occur in other conditions at this age.

Other Features.—Enlargement of the spleen, according to some observers, is found in many cases. Distention of the veins of the neck is often associated with increased intracranial pressure and is an especially valuable sign in cases of increased pressure in which no bulging of the fontanel is apparent.[17]

Comment.—From the foregoing consideration it is evident that the classic signs of meningitis are usually absent in the new-born. It is difficult to single out from the foregoing list of signs and symptoms the ones that are most common and indicative of meningitis in early infancy. The least specific among these, however, may be just the ones which will indicate its presence. Thus, an irregular fever in the presence of intestinal disturbances which appeared without any demonstrable cause and which do not respond readily to treatment, is highly suggestive of meningitis and presents an indication for lumbar puncture. In addition, hyperesthesia, a bulging fontanel, distention of the veins of the neck, incessant crying or a dissociation between the pulse rate and the temperature should by itself be presumptive of meningitis in a young infant.

ETIOLOGY AND PATHOGENESIS

Meningococcic Meningitis.—The pathogenesis in young infants differs only a little from that in older children. The portal of entry and the mode of invasion remain in many cases as puzzling as in adults. In the majority of cases investigations as to the possible source of infection or even bacteriologic examination of the nasopharynx of suspected persons with whom the infant has been in contact have failed to reveal any causal relationship or source of infection. However, a more thorough epidemiologic and bacteriologic investigation of all possible contacts

17. Neal, Josephine B.: Arch. Pediat. **38**:1 (Jan.) 1921.

might occasionally disclose the source of infection by contact or from a carrier.[18] In some of the cases in the new-born, infection may be traced to the methods of resuscitation by mouth-to-mouth or catheter suction.[3] Here then, as in older children and adults, it must be assumed that the source of infection is through contacts and carriers and that the usual portal of entry is through the mouth and the nasopharynx. The route of invasion and spread is most likely through the blood stream with subsequent selective localization in the pia-arachnoid of the brain and the spinal cord. (The best illustration of the hematogenous mode of spread was presented in the interesting case described by Gradwohl [19] in 1899, in which infection was intra-uterine.)

Nonmeningococcic Meningitis.—A variety of organisms have been recorded. Of these, the streptococcus, the staphylococcus and the pneumococcus cause meningitis that in no way differs from the meningitis of later life. They occur mostly as secondary invaders following otitis media, abscess of the brain or trauma, by blood transmission in pneumonia, in spina bifida, whether an operation is performed or not, or from other distinct foci of suppuration. Pneumococcic meningitis may also be primary when preceded by follicular tonsillitis or by rhinopharyngitis or by infection through carriers. Meningitis due to Bacillus influenzae, though rarer, has also been reported in infants less than 3 months of age, occurring in from 0.6 to 0.8 per cent of all such cases.[20] Tuberculous meningitis is also relatively rare at this age (1.3 per cent of patients less than 3 months of age in Holt's series [21]). Gonococcic meningitis as a sequela of ophthalmia has also been reported in the new-born.[22] Among the many other invaders are Bacillus mucosus-capsulatus, Bacillus lactis-aerogenes, Bacillus pyocyaneus and Bacillus acidi-lactici.[23] Among the rarer organisms may be mentioned Bacillus

18. Worster-Drought, C., and Kennedy, Alex Mills: Cerebro-Spinal Fever: Etiology, Symptomatology, Diagnosis and Treatment of Endemic Cerebro-Spinal Meningitis, London, A. & C. Black, 1919, p. 58. Mathias, Ernst: Zentralbl. f. Gynäk. **54**:3074 (Dec.) 1930.

19. Gradwohl, R. B. H.: Philadelphia M. J. **4**:445 (Sept. 2) 1899.

20. (*a*) Wollstein, M.: Influenzal Meningitis and Its Experimental Production, Am. J. Dis. Child. **1**:42 (Jan.) 1909. (*b*) Neal, J. B.: Internat. Clin. **4**:1, 1918.

21. Holt, L. Emmett: Observations in Three Hundred Cases of Acute Meningitis in Infants and Young Children, Am. J. Dis. Child. **1**:26 (April) 1911.

22. Bradford, W. L., and Kelley, H. W.: Gonococcic Meningitis in a New-Born Infant: With Review of the Literature, Am. J. Dis. Child. **46**:543 (Sept.) 1933.

23. Bonhoff, H., and Esch, P.: Ztschr. f. Geburtsh. u. Gynäk. **70**:886 (Sept.) 1912. Scheib.[14] Benfey, A.: Med. Klin. **50**:1199, 1907. Debré, R.; Semelaigne, G., and Broca, R.: Méningo-épendymite suppurée ou pyocéphalie du nouveau-né, Nourrisson **19**:246 (July) 1931.

typhosus [24] and Bacillus paratyphosus or related organisms.[25] Syphilitic meningitis also has been observed in infants 3 months of age.[26]

The organisms may gain entrance by way of any of the following organs: the eye and orbit, ear, nasopharynx, buccal cavity, gastrointestinal tract, umbilicus, genitalia, spina bifida and skin and the mother's external and internal genitalia. Hereditary syphilis also is an important contributory factor. The mode of spread is direct or through secondary hematogenous invasion and is not specific for infants or the new-born.

In contrast to infection with the majority of the aforementioned organisms, meningitis due to B. coli and related organisms appears to be distinctive and peculiar to the new-born and to infants in the first two or three months of life and is rarely seen in older infants or children. In older children this organism is a constant saprophytic inhabitant of the intestinal tract and rarely becomes pathogenic. In a review of cases of meningitis in infants under 3 months of age, Barron [2] found that 33 per cent of these were caused by B. coli. Karplus [8] also found that 30 per cent of the cases in her series had been caused by B. coli. The same high incidence of meningitis due to B. coli in early infancy was found by other authors, notably by Fothergill and Sweet,[27] 7 of whose 9 cases occurred in infants between 1 and 5 weeks of age.[28] In these cases no other lesions were found outside the central nervous system. It is in this type of case that the study of the portal and mode of entry and of the pathogenesis is extremely interesting and does not lack in hypotheses and speculations. In many cases the authors admitted that the manner in which the organisms were propagated was quite unknown. Others attempted to explain it in various ways, as by the aspiration or the swallowing of contaminated amniotic fluid in premature respiration or in partial asphyxiation, by infection from bathing water, by infection from the finger of the obstetrician or of the accoucheur, by infection from purulent metritis of the mother or through circumcision.[29] This does not, however, explain entirely the high incidence of meningitis due to B. coli and allied organisms as con-

24. Dukakis, Panos S.: Typhoid Meningitis in a Two Months Old Baby, J. A. M. A. **89**:2257 (Dec. 31) 1927.

25. Arzt, L., and Boese, J.: Wien. klin. Wchnschr. **21**:217, 1918. Rieper: Virchows Arch. f. path. Anat. **289**:301, 1933. Lyall, Harold L.: J. M. Research **27**:457, 1913.

26. Amesse, J. W., and Barber, W. W.: Am. J. Syph. **11**:544, 1927.

27. Fothergill, Le Roy D., and Sweet, L. K.: J. Pediat. **2**:696 (June) 1933.

28. This, however, is not in accord with the view and experience of Neal (Am. J. M. Sc. **172**:740 [Nov.] 1926).

29. (*a*) Herman, C.: Arch. Pediat. **33**:384, 1915. (*b*) Scherer: Jahrb. f. Kinderh. **39**:1, 1895. (*c*) Noeggerath, C. F.: München. med. Wchnschr. **54**:617, 1907. (*d*) Hinsdale, Guy: Am. J. M. Sc. **118**:250, 1899.

trasted with its extreme rarity in older children and adults. Other factors must be looked for in order to explain it, as was well brought out by Barron [2] and especially by Cooke and Bell [6] in their discussions on the same topic. B. coli and its allied organisms are among the many nonpathogenic bacteria to which the gastro-intestinal tract is normally especially permeable. Ribbert showed that bacteria are always to be found in the mesenteric glands of animals. Ford [30] found that bacteria are frequently found in such organs as the liver and kidney, especially at the height of digestion. Micro-organisms have been demonstrated also in the lymph during digestion.

In the light of these observations it is easy to explain the normal presence in human serum of various agglutinins for many types of bacteria as the result of acquired active immunity. Of such bacteria B. coli is an outstanding example. Another interesting fact is that the normal agglutinin for B. coli is found in a much higher quantity in the blood of adults than in that of the young and—what is most significant—that in the blood of fetuses and of the new-born this agglutinin is absent. Coupled with this are the observed phenomena of the increased permeability of the gastro-intestinal mucosa of the extremely young to bacteria and to foreign proteins. Therefore, when organisms such as B. coli accidentally and suddenly gain access to the body of a new-born infant they meet with no resistance on the part of the host because of the lack of acquired immunity. The mode of spread of the infection through the blood with ultimate selective localization in the pia-arachnoid of the brain and of the cord must be surmised as in the case of infection with the meningococcus.[31] The aforementioned factors may thus best explain the especially high incidence of meningitis caused by B. coli and the allied organisms in the new-born and in young infants and its great rarity in older children and adults.

PATHOLOGY

The anatomicopathologic findings in all types of meningitis present in general nothing specific for the new-born and the young infant. Attempts have been made to establish some distinguishing anatomic features between the various forms of acute meningitis, but, as pointed out by Hassin,[32] this is exceedingly difficult if not impossible. As the

30. Ford, W. W.: Text-Book of Bacteriology, Philadelphia, W. B. Saunders Company, 1927, p. 893.

31. The best proof of the hematogenous mode of spread in B. coli meningitis is presented in a recent work by Fothergill and Sweet,[27] who were successful in isolating the organisms during life from the blood as well as from the spinal fluid in about 85 per cent of infants with meningitis, the greatest majority of whom were between 1 and 5 weeks of age.

32. Hassin, G. B.: M. Rec. **93**:760 (May 4) 1918.

features are in general not distinctive to the new-born, they will not be dwelt on here. One may mention only that the meningeal involvement in the brain and in the spinal cord at this age is as widespread as it is in older children. Adhesions and blockage of the circulation of the cerebrospinal fluid with secondary hydrocephalus also develop early and are not as rare as is thought by some authors.

PROGNOSIS

Meningococcic Meningitis.—The prognosis in the first three months of life is exceedingly poor. "As far as we know," wrote N. O. Pearse in Abt's "Pediatrics" in 1923 on meningitis in the new-born, "no recoveries have occurred." Recoveries are believed to be so rare that reports of single cases have appeared in the literature even recently. The impression is gained, however, that, just as the frequency of meningococcic meningitis in early infancy is higher than is commonly thought, so is the percentage of recoveries from it much larger than it is usually believed to be. The mortality in the first three months of life is given as 48 per cent and higher. This high rate is chiefly due to delay in the institution of treatment, which is a direct consequence of the difficulty in establishing a correct diagnosis. Other factors are the poor resistance of nursing infants to infective agents in general, the frequency of pneumonia as a complication and the tendency for a blockage of the circulation of cerebrospinal fluid to form as a sequela of basilar meningitis.

Nonmeningococcic Meningitis.—The usual impression is that the mortality in general, whether in nurslings, older children or adults, is almost 100 per cent. However, as is seen from occasional reports in the literature, the prognosis is not always immediately or altogether hopeless. Koplik [3] reported a case of meningitis due to B. coli in a new-born child in whom hydrocephalus developed and who died at the age of 16 months of asthenia and optic necrosis. Reports of cure in cases of staphylococcic meningitis are also encountered in the literature.[33] Even in cases of pneumococcic meningitis a number of instances of recovery are on record.[34] There are also reports of spontaneous recovery from pneumococcic and other types of meningitis.[35] Although most

33. (*a*) Lamb, F. H.: Arch. Pediat. **45**:306 (Feb.) 1928. (*b*) Goldberg, B. I.: Boston M. & S. J. **192**:350 (Feb. 19) 1925; quoted by Lamb.[33a] Cases have been reported by others also.

34. (*a*) Rosenow, George: Deutsche med. Wchnschr. **46**:9 (Jan. 1) 1920. (*b*) Globus, J. H., and Kasanin, J. I.: Pneumococcus (Type IV) Meningitis; Report of a Case Treated by Forced Subarachnoid Drainage, with Recovery, J. A. M. A. **90**:599 (Feb. 25) 1928. Other writers have also reported cases.

35. Uhr, J. S.: Arch. Pediat. **46**:121 (Feb.) 1929.

of the cases that have been cited were in older children and adults, they are worthy of mention here because of the new hope that they bring to the grave prognosis of pyogenic meningitis in general.

DIAGNOSIS

The diagnosis of meningitis in the new-born and in young infants, as shown previously, is extremely difficult. No pathognomonic signs and symptoms are found at this age, and exceedingly few objective signs are present that can be elicited with any degree of constancy. Stiffness of the neck and the Kernig sign are often so slight as to be unappreciable. The Brudzinski sign and the action of the reflexes are unreliable. The temperature curve has no special characteristics. Convulsions, though present in a high percentage of cases, can be seen also in other afflictions at this age. Little wonder, then, that meningitis at this age is so often not recognized and the condition wrongly diagnosed as food poisoning, acute gastro-enteritis, marasmus or congenital debility. Thus, even by a competent physician the diagnosis of meningitis may not be reached before the lapse of considerable time, and sometimes it is not made even after many days of observation in the hospital.

As no special pathognomonic signs are found, it is impossible to establish any definite diagnostic criteria. However, as previously mentioned, from the signs and symptoms that are highly suggestive of meningitis at this age the following may be singled out: hyperesthesia, irritability or somnolence, crying, convulsions, tenseness or bulging of the fontanel, distention of the veins of the neck and gastro-intestinal disturbances of any sort. The presence of the gastro-intestinal disturbances is highly significant.

At present the most reliable diagnostic method is of course spinal puncture, and it must be resorted to rather frequently. The various diagnostic problems that are connected with this procedure as well as with the characteristics of the spinal fluid itself are not distinctive of meningitis of early infancy and will therefore not be discussed here.[36]

A valuable aid in the diagnosis of meningococcic meningitis even before the brain is invaded is offered by the detection of the organisms in cutaneous lesions in the petechial eruption, when this is present.[37]

In the differential diagnosis the condition that for practical purposes must be thought of most is intracranial hemorrhage. In cases of this

36. It may be added in this connection that an absolute diagnosis of the type of meningitis can be reached only by bacteriologic and serologic methods and not tinctorially. Neglect with regard to this point has brought not a little confusion in the literature.

37. McLean, Stafford, and Caffey, John P.: Endemic Purpuric Meningococcus Bacteremia in Early Life, Am. J. Dis. Child. **42**:1053 (Nov.) 1931.

condition, however, when the picture is clearcut there is usually no fever, and if convulsions occur once they may not be repeated. The fontanel has a boardlike feeling and does not become more prominent with the advance of the disease. There are usually other associated symptoms, such as cyanosis, irregular respiration and apnea. Furthermore, the spinal fluid may be bloody.

The differential diagnosis between the various types of meningitis in early infancy can be dismissed briefly, for, as was pointed out previously, the symptomatology in at least the primary forms is essentially the same in meningitis that is caused by the meningococcus as in meningitis that is caused by any other organism.

In conclusion, then, because of the pitfalls and uncertainty of the diagnosis of meningitis at this age, one must adopt the rather radical view of most observers, namely, that whether during an epidemic or not, whenever the diagnosis is obscure or an infant is sick without an apparent discoverable cause, meningitis is to be thought of and the indication for a spinal puncture then clearly presents itself.

TREATMENT

Meningococcic Meningitis.—Treatment for young infants differs in no way from that for older infants, children or adults and therefore will not be elaborated on here. Some authors have gone to great trouble to devise special tables for the regulation of the dosage of serum in accordance with age, but this, as pointed out by Neal,[20b] is entirely unnecessary. The main criterion to follow is not to increase the intracranial pressure unduly, and to gage the quantity of serum to be injected with that of the cerebrospinal fluid that can be withdrawn, or in accordance with the ease with which the injected serum flows in by gravity. The conservative line of treatment is the best one to follow, for too intensive serum therapy results in a higher percentage of untoward effect and in a higher mortality.[16b] The routine schedule to follow is to make a lumbar puncture daily, to remove as much fluid as possible and to inject serum by gravity. It is best to inject a slightly smaller amount of serum than the amount of spinal fluid withdrawn. If 20 cc. of fluid or more is removed, a similar quantity of serum may be injected daily. If the amount of fluid removed is extremely small, a greater quantity of serum may be injected. The same procedure can be followed even when the tap is entirely "dry." Only when signs point definitely to blockage of the circulation of the cerebrospinal fluid or when the fluid does not flow well is it necessary to resort to the ventricular or the cisternal route. These methods, however, should be restricted to these complications alone, because they present the danger of secondary infection and the possibility of later mental impairment and show a smaller

number of recoveries (Neal [16b]). In this connection it should be mentioned that great care must be exercised in the performance of spinal or ventricular puncture or injection of serum in young infants as most of the fatal accidents in these procedures have occurred in infants less than 1 year of age. It must also be said that this danger should not in the slightest degree detract from the life-saving importance of spinal puncture. One cannot, therefore, overemphasize the maxim of Netter and Debré [38] that whenever there is any doubt of the correct diagnosis or when the diagnosis is vague, it is safest to resort to a spinal puncture rather than to temporize or follow a symptomatic therapy. Aside from the specific serum therapy the usual plan of treatment of any acute infection should, of course, be followed.

Nonmeningococcic Meningitis.—This phase of nonmeningococcic meningitis, in the light of the usually accepted views and reports as to its futility, could at first thought be dismissed briefly. However, in recent years a number of reports have appeared in the literature of cures obtained in cases of septic meningitis by means of different methods and agents. Thus, administration of optochin hydrochloride and antipneumococcus serum or cerebral-cisternal-spinal lavage was used in pneumococcic meningitis,[39] injections of gentian violet or a bacteriophage in staphylococcic meningitis [40] and injection of antistreptococcus serum, surgical intervention or spinal drainage in streptococcic meningitis (Applebaum [41] and others). Attempts, though not as yet entirely successful, have been made in cases of meningitis due to B. influenzae as well (Ward and Fothergill [42] and others). (It must be added that in evaluating the efficacy of any new line of treatment in nonmeningococcic meningitis the possibility of spontaneous recovery must be borne in mind; the patient must also be watched for some time before he is finally pronounced cured.)

No attempt is made here to review all the cases of pyogenic meningitis in which the various forms of treatment were instituted. The cases just cited, most of which occurred in older patients, were mentioned because they forecast a new and hopeful line of attack in the treatment

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38. Netter, Arnold, and Debré, Robert: La méningite cérébro-spinale, Paris, Masson & Cie, 1911, p. 282.

39. Clark, J. G.: Lancet **2**:1330 (Dec. 17) 1932. Rosenow and Globus and Kasanin.[34] Uhr.[35]

40. Lamb.[33a] Globus and Kasanin.[34b] Noeggerath.[29c]

41. Applebaum, E.: Streptococcic Meningitis, J. A. M. A. **98**:1253 (April 9) 1932.

42. Ward, H. K., and Fothergill, L. D.: Influenzal Meningitis Treated with Specific Antiserum and Complement; Report of Five Cases, Am. J. Dis. Child. **43**:873 (April) 1932.

of nonmeningococcic meningitis in general and of that occurring in early infancy in particular, which up to now has been considered as almost entirely futile.

SUMMARY AND CONCLUSIONS

Meningitis in the new-born and in young infants is characterized by being atypical, protean and masked in its clinical manifestations.

The diagnosis is often missed and the condition mistaken for acute gastro-enteritis, congenital debility, marasmus, tetany, etc.

Illustrative cases are reported in which signs of involvement of the central nervous system were scant or absent and in which the clinical picture centered around the gastro-intestinal or respiratory systems.

A review of the literature on this subject was made which emphasized the relative rarity of meningitis at this age. A statistical study of all cases of meningitis in children during a four year period at the New York Post-Graduate Medical School and Hospital showed that only 2.5 per cent of the cases of the meningococcic and 4.1 per cent of those of the nonmeningococcic variety occurred in infants 3 months of age and younger.

The clinical picture as it differs from that in older children and in adults is given in detail. In the absence of pathognomonic signs and when meningeal signs are not found, the following nonspecific signs and symptoms may be suggestive of meningitis: an irregular fever in the presence of gastro-intestinal disturbances of any sort which occur without any demonstrable cause and which do not respond readily to treatment; in addition, hyperesthesia, irritability, somnolence, tenseness or bulging of the fontanel, distention of the veins of the neck, incessant crying and a dissociation between the pulse and respiratory rates and the temperature.

The pathogenesis of meningococcic and nonmeningococcic meningitis is discussed. The various portals and modes of entry, and sources and means of spread of infection are cited. The different causative organisms of pyogenic meningitis and their relative frequency are reviewed.

The prevalence of meningitis due to B. coli and related organisms in the new-born and its rarity in older children is emphasized, and explanatory factors are cited.

The anatomicopathologic features are practically the same in the new-born as in older children.

The prognosis of all forms of meningitis, especially of the pyogenic varieties at this age, is extremely poor. Mortality figures for each variety are given, the lowest being for meningococcic meningitis, which is 48 per cent or higher. The high mortality from meningococcic meningitis

is due mainly to the difficulty of diagnosis and the delay in the institution of treatment. Cases of recovery from nonmeningococcic meningitis that was spontaneous or that followed specific or nonspecific treatment are cited from the literature.

A diagnosis in the absence of any pathognomonic signs is extremely difficult. Some of the signs and symptoms that may be helpful are cited. The most reliable diagnostic method is still spinal puncture, and it should be resorted to frequently.

The treatment of meningococcic meningitis in the new-born and in young infants is the same as in older children, the conservative line of treatment being the safest and best one to follow. The ventricular and cisternal routes should not be used indiscriminately and should be resorted to only in event of blockage of the circulation of the cerebrospinal fluid. Treatment of nonmeningococcic meningitis is less encouraging, but there are nevertheless some indications that new methods of treatment forecast a more favorable progress in this variety also.

Pediatric Biographies

WILLIAM JOHN LITTLE
1810-1894

A NOTE ON THE HISTORY OF SPASTIC DIPLEGIA

JOHN RUHRÄH, M.D.†
BALTIMORE

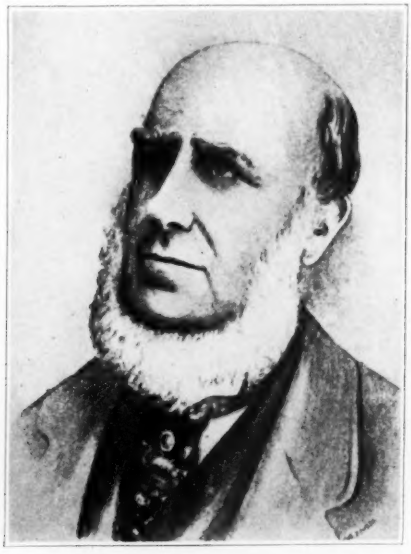
William John Little was born in East London in 1810; as a child he was not strong and suffered from numerous ailments, including infantile paralysis which left him with a clubfoot. He was sent to St. Margaret's School at Dover, where he made a good record and acquired a knowledge of French, so that three years later he was sent to the College of St. Omer in France. There he won a prize for French composition, being the first Englishman to be so honored. At 16 he returned to London and was apprenticed to an apothecary near the place where he was born. At 18 he decided to study medicine and entered the London Hospital. In 1831 he became a licentiate of the Apothecaries Company, and the next year he was admitted to membership in the Royal College of Surgeons. In 1836 he became lecturer on comparative anatomy and physiology in the London Hospital Medical School.

He settled in Billiter Street and later went to Newcastle to study Asiatic cholera, which had made its appearance there. He then went to France to see Delpech, who had introduced tenotomy in the treatment of clubfoot, but that surgeon was afraid to operate on him, fearing infection. He proceeded to Berlin, where he studied under Johannes Müller and came in contact with such men as Henle, Schwann, Remak and others. He then went to Hannover to consult Strohmeyer, who was performing successful tenotomies, and was operated on himself with a good result. He returned to Berlin and operated on thirty patients for clubfoot. This experience, together with his pathologic studies, furnished the material for his thesis "Symboliae ad talipedum varum cognoscendi," which he presented for his degree of doctor of medicine in 1837. The same year he was made a licentiate of the Royal College of Physicians. The membership had not been instituted at that time. In 1839 he published "Clubfoot and Analogous Distortions," in which he included histories of congenital and acquired cases. The latter were due to poliomyelitis, but Little apparently did not recognize this.

† Deceased.

It remained for Jacob Heine to write the first monograph on the subject. In 1843 Little published "Ankylosis or Still Joint."

Following this he established the Orthopaedic Institution, now the Royal Orthopaedic Hospital. In 1844 he gave up his work in it and was made lecturer on medicine; in 1845 he became physician to the London Hospital and served until 1863. He was a visiting physician to the Asylum for Idiots at Earlswood and the Infant Orphan Asylum. In 1853 he published what he regarded as his greatest work, "On Deformities of the Human Frame." In this he described two cases of pseudohypertrophic paralysis, but at that time the condition was not so named.



WILLIAM JOHN LITTLE
1810-1894

It remained for Duchenne of Boulogne to make a more thorough study of it. Little's work also contained a description of spastic diplegia, which is known as Little's disease. In 1868 he brought out a book, "On Spinal Weakness and Spinal Curvature."

He suggested the use of injections or transfusions of saline solution in cases of Asiatic cholera and also a number of other things. He was the first to perform tenotomy of the tibial tendon, Strohmeyer having confined his work to the achilles tendon. Little was much honored and beloved and shone not as a lecturer but as a teacher. He left London in 1884 and retired to the country, where he had a house at Walthamstow; later he moved to Kent. He died after a short illness in 1894.

Little's first contribution on spastic diplegia appeared in the *Lancet* [1] and is in part as follows:

. . . In many instances the spasmodic affection is produced at the moment of birth, or within a few hours or days of that event. In the majority of the cases of universal contracture of the upper and lower extremities which have fallen under my observation, the subjects were born at the seventh month, or prior to the end of the eighth month of uterogestation. In two cases the birth occurred at the full period of gestation, but owing to the difficulty and slowness of parturition the individuals were born in a state of asphyxia, resuscitation having been obtained, at the expiration of two and four hours, through the persevering efforts of the accoucheurs. The fact of the greater liability to universal spasmodic contraction of infants prematurely born is susceptible of two explanations. I have ascertained that the premature labours in question were rarely induced by mechanical injury or sudden application of other causes, such as excessive exertion of a violent emotion, but were consequent on derangement of the health of the parent of some duration. One explanation, therefore, suggests itself, that the deteriorated health of the parent had directly impaired the nutrition of the foetus, and both directly and indirectly the healthy development of the nervous system of the foetus, creating a susceptibility to disease.

The second explanation that I may offer you, and one especially applicable to those cases of contracture concerning which doubt exists whether the spasmodic affection originated prior or subsequently to birth, is based upon the proposition that an infant, prematurely born, is, although in a normal stage of development, inadequately prepared to contend against the operation of external agents. The respiratory and circulatory organs of an infant under these circumstances are ill suited to the proper aëration of the blood, and its due transmission throughout the frame; the alimentary organs cannot yet be perfected for the elaboration of chyle, and the incomplete development of the nervous system must interfere with the assimilation of nutritive matter for the wants of the economy. It cannot occasion surprise that altered function, congestion, or disease of the most susceptible of the infant's organs, those of the nervous system, should occur. Hence the production in some cases of transient muscular contraction—convulsions and death; and in others of permanent spastic contractions in various parts of the body, succeeded by the forms of contracture under consideration.

Little's second and complete article was presented to the Obstetrical Society by Dr. Tyler Smith and is to be found in the *Transactions of the Obstetrical Society*.[2] It is a long thorough study, and the following quotations constitute the most important parts:

ON THE INFLUENCE OF ABNORMAL PARTURITION, DIFFICULT LABOURS, PREMATURE BIRTH AND ASPHYXIA NEONATORUM, ON THE MENTAL AND PHYSICAL CONDITION OF THE CHILD, ESPECIALLY IN RELATION TO DEFORMITIES.

By W. J. LITTLE, M.D.

SENIOR-PHYSICIAN TO THE LONDON HOSPITAL; FOUNDER OF THE ROYAL ORTHOPEDIC HOSPITAL; VISITING-PHYSICIAN TO ASYLUM FOR IDIOTS, EARLSWOOD; ETC.

(Communicated by Dr. Tyler Smith.)

1. Little, W. J.: Lancet **1**:319, 1844.
2. Little, W. J.: Tr. Obst. Soc. London **3**:293, 1862.

PATHOLOGY has gradually taught that the foetus in utero is subject to similar diseases to those which afflict the economy at later periods of existence. This is especially true if we turn to the study of the special class of abnormal conditions, which are termed deformities. We are acquainted, for example, with abundant instances of deformities arising *after* birth from disorders of the nervous system—disorders of nutrition, affecting the muscular and osseous structures,—disorders from malposition and violence. Each of these classes of deformity has its representative amongst the deformities which originate before birth, viz., congenital clubfoot, congenital rickets, congenital degenerations of muscles, amputations in utero from strangulation by umbilical cord or adventitious bands, intrauterine fractures, &c.

. . . Thirty-five years ago the pathology of deformities, if not invested with fable, was wrapped in obscurity; it was then scarcely perceived that the materials for extensive inductive observation existed.

Nearly twenty years ago, in a course of lectures published in the "Lancet," and more fully in a "Treatise on Deformities," published in 1853, I showed that premature birth, difficult labours, mechanical injuries during parturition to head and neck, where life had been saved, convulsions following the act of birth, were apt to be succeeded by a determinate affection of the limbs of the child, which I designated spastic rigidity of the limbs of new-born children, spastic rigidity from asphyxia neonatorum, and assimilated it to the trismus nascentium and the universal spastic rigidity sometimes produced at later periods of existence. . . . . . It is obvious that the great majority of apparently stillborn infants, whose lives are saved by the attendant accoucheur, recover unharmed from that condition. I have, however, witnessed so many cases of deformity, mental and physical, traceable to causes operative at birth, that I consider the subject worthy the notice of the Obstetrical Society. In orthopedic practice alone, during about twenty years, I have met with probably two hundred cases of spastic rigidity from this cause. I omit reckoning the subjects of idiot and other asylums, in which probably such cases abound, but of which I have been able to obtain no history. I revert to the subject at the present moment because I believe I am now enabled to form an opinion of the nature of the anatomical lesions and the particular abnormal event at birth on which the symptoms depend. . . .

. . . The former class of affections may be described as impairment of volition, with tonic rigidity and ultimately structural shortening, in varying degrees, of a few or many of the muscles of the body. Both lower extremities are more or less generally involved. (See Plate.) Sometimes the affection of one limb only is observed by the parent, but examination usually shows a smaller degree of affection in the limb supposed to be sound. The contraction in the hips, knees, and ankles, is often considerable. The flexors and adductors of thighs, the flexors of knees, and the gastrocnemii, preponderate. In most cases, after a time, owing to structural shortening of the muscles and of the articular ligaments, and perhaps to some change of form of articular surfaces, the thighs cannot be completely abducted or extended, the knees cannot be straightened, nor can the heels be properly applied to the ground. The upper extremities are sometimes held down by preponderating action of pectorals, teres major and teres minor, and latissimus dorsi; the elbows are semi-flexed, the wrists partially flexed, pronated, and the fingers incapable of perfect voluntary direction. Sometimes the upper extremities appear unaffected with spasm or want of volition, sometimes a mere awkwardness in using them exists. Not infrequently the parent reports that the hands were formerly affected. Participation of the muscles of trunk is sometimes shown by the shortened, flattened aspect of pectoral and abdominal surfaces, as compared

with the more elongated and rounded form of the back. The prominence of back partially disappears on recumbency, but the greater weakness of muscles on dorsal aspect of trunk is obvious when the individual again attempts to sit upright. The muscles feel harder than natural to the age. Micturition is sometimes observed to be rare, and the bowels usually confined, either from deficient exercise of voluntary expulsive power or from implication of the sphincters. The muscles of speech are commonly involved, varying in degree from inability to utter correctly particular letters up to entire loss of articulating power. Sometimes articulation is only slow and difficult, like other acts of volition, the child or adult reminding

Spastic diplegia. The original illustration (plate VI) used by Little in his article in the Transactions of the Obstetrical Society.

us of a tardigrade animal. Sometimes the speech is nervous, impulsive or stuttering. Often during the earliest months of life deglutition is impaired, and the power of carrying saliva into the fauces is not acquired until late. The intellectual functions are sometimes quite unaffected, but in the majority of cases the intellect suffers—from the slightest impairment which the parent unwillingly acknowledges or fails to perceive up to entire imbecility. The functions of organic life are unexceptionably performed, except, perhaps, that of development of caloric, although the depression of temperature in later life is more probably dependent upon the want of proper exercise. The frame is often lean and wiry, but not wasted. On the contrary, it is generally well nourished. The appetite is good,

the child is often described as the healthiest of the family. These subjects often lead a more precarious existence during the first weeks after birth, at first even vegetative existence languishes, sometimes, perhaps, because premature birth or difficult labour, by impairing the maternal supply of nutriment, renders more difficult the infant's recovery from the shock its system received at birth. However, in the majority of instances, after restoration of the vegetative functions, a gradual but slow amelioration of all the functions of animal life is perceived. Some cases present distinct convulsive twitchings of face or limbs during first days after birth, open or suppressed convulsions, opisthotonos, or laryngismus. In some instances

Spastic diplegia. Plate VII in the aforementioned article.

the persistent rigidity of muscles commences or is observed shortly after birth, in others it escapes observation until the lapse of some weeks or months. The child's limbs are sometimes reported to have been simply weaker, to have shared in the general debility, the question of viability having alone occupied the attention of the attendants during the first month. Occasionally the weakness of the limbs has been recognized as a genuine paralysis in the first instance, of which the rigidity of muscles has been the sequel. Before the age of three or four months, though sometimes in slight cases not until ordinary time for walking arrives, the nurse perceives that the infant never thoroughly straightens the knees, that these cannot be properly depressed or separated, that she is unable to wash and dress the infant with the ordinary facility, that the hands are not properly used. The upper

extremities recover before the lower limbs. Sometimes the trunk is habitually stiffened, so that the infant is turned over in the lap "all of a piece," as the nurse expresses it. Occasionally the head is habitually retracted. Where the symptoms of convulsions or "inward convulsions" exists, the rigidity is attributed to the convulsions. In many cases convulsions have been absent. As the child approaches the period at which the first attempts at standing and progression should be made, it is observed to make no use of the limbs, or he is incapable of standing except on the toes, or the feet are disposed to cross each other. Even children slightly affected rarely "go alone" before three or four years of age, many are unable to raise themselves from the ground at that age, and others do not walk, even indifferently, at puberty. On examination, the surgeon finds that the soles of the feet are not properly applied to the ground, that the knees always incline inwardly, and continue bent. When locomotion is accomplished, the movements are characterised by inability to stand still and balance the body in erect attitude. In the best recoveries from *general* spastic rigidity, even in the adult, the gait is shuffling, stiff; each knee, by forcible spastic rubbing against its fellow, obstructs progression.

The external form of cranium occasionally exhibits departure from the normal or average type, such as general smallness of skull, depression of frontal or occipital region only, sometimes one lateral half of skull, sometimes of one half of occiput, or forehead only. In slight cases the head has been well developed.

In cases even with great inertia as to exercise of volition in any part of the body, common sensibility appears little, if at all, deficient. The child often, indeed, manifests uncommon sensitiveness to external impressions, even when approaching adolescence he is alarmed at trifling noises. The sleep after the first weeks of life is light, easily disturbed. Often there is extreme sensibility to touch, the whole condition reminding the observer of tetanus. In a few cases a distinct resemblance to severe chorea is perceptible. It is probable that some of the cases designated by authors congenital chorea have been cases of the affection I have described. . . .

. . . A survey of the history of forty-seven cases, appended, shows that one fact is common to all the cases of persistent spastic rigidity of new-born children, namely, that some abnormal circumstance attended the act of parturition, or rather, the several processes concerned in separating the foetus from the parent and its establishment in the world as an independent being. I cannot recall positively to mind, or find recorded in my journals, more than a single case in which this persistent *spastic* rigidity affected a numerous series of muscles of the trunk and extremities which could be unequivocally referred to any illness subsequent to the establishment of proper pulmonary respiration as its starting point. Often it has been found that convulsions in infancy had occurred, to which the disease had been attributed. Spastic contraction of a single set of muscles, as the gastrocnemii of one or both limbs, commonly of one limb only, or of the muscles, of the forearm and calf on one side, is certainly an everyday occurrence after infantile convulsions, convulsions *during* dentition, and during early childhood without convulsions or other marked illness. But general spastic rigidity I have, with one exception, found to have been preceded by some abnormal act connected with mode of birth. . . .

Pediatrics in Art

INFANTILE EDEMA

JOHN RUHRÄH, M.D.
BALTIMORE

If the illustration showing the Santa Famiglia de Mino da Fiesole, the original of which is now in Florence, does not show an infant with edema it certainly presents a good imitation of it. The swollen turgid

Infantile edema.

legs and feet, the ascites and the lesser involvement of the upper part of the body are all indicative. The skin is stretched and most but not all of the normal folds are obliterated. This condition is more marked than it would be in a case of obesity. Note the normal hands. Why an artist should have chosen such a child for a model is a matter of conjecture.

The Madonna shows a slight enlargement of her thyroid. St. John the Baptist, in the background, albeit well nourished, seems normal.

News and Comment

SOCIETY NEWS

Arkansas State Pediatric Association.—On March 6, under the able direction of Dr. Morgan Smith of Little Rock, with the blessing of Dr. E. C. Mitchell of Memphis, Tenn., the Arkansas State Pediatric Association was launched.

American Pediatric Society.—At the meeting of the American Pediatric Society, held at the Wade Park Manor Hotel, Cleveland, on May 2 to 4, the following officers were elected:

President, Dr. Fritz B. Talbot, Boston
Vice-president, Dr. Franklin P. Gengenbach, Denver
Secretary-treasurer, Dr. Hugh McCulloch, St. Louis
Editor-recorder, Dr. Heyworth N. Sanford, Chicago.
Member of the Council, Dr. C. Anderson Aldrich, Winnetka, Ill.

The following were elected to active membership:

Dr. W. W. Swanson, Chicago
Dr. Joseph A. Johnston, Detroit
Dr. John A. Toomey, Cleveland
Dr. Lewis Webb Hill, Boston
Dr. Edwards A. Park, Baltimore
Dr. A. H. Parmelee, Chicago

The following were elected honorary members:

Dr. Johann Bokay, Budapest, Hungary
Dr. Leonard Parsons, Birmingham, England.

UNIVERSITY NEWS

Summer Session in Child Development.—The University of Iowa announces its summer session in child development and parent education from June 10 to August 22. The tuition is $36 for the first term and $30 for the second. Requests should be sent to the Summer Session Office, 117 University Hall, Iowa City.

This instruction is given by members of the faculty at the University of Iowa, together with some teachers from other institutions. The courses include instruction in both the physical and the psychic side of the child in its social and economic relations, as well as some work in education and child welfare.

Course in Correction of Speech Disorders, Emerson College.—Emerson College, in its summer session, will offer a course in "Correction of Speech Disorders." To candidates holding a Bachelor's degree, a certificate of capability to practice in the field of speech correction will be issued. The full course will be offered in four successive summers. For information address The Registrar, Emerson College, 130 Beacon Street, Boston.

PERSONAL

Dr. H. E. Coe has been chosen chief of the staff, and Dr. J. I. Durand, chief of the pediatric department, of the Children's Orthopedic Hospital in Seattle.

Dr. Adolph G. De Sanctis has been appointed director of the department of pediatrics of the New York Post-Graduate Medical School and Hospital, Columbia University.

Dr. Ethel C. Dunham, associate clinical professor of pediatrics at Yale University School of Medicine, has been named acting director of the Division of Maternal and Child Health of the United States Children's Bureau.

DEATHS

Prof. Abele Subizarreta, a well known Argentine pediatrician, died recently at the age of 65.

Dr. Ernest Lackner, for many years on the pediatric staff of the Sarah Morris Hospital for Children (Michael Reese Hospital), Chicago, died on March 14 at the age of 83.

CORRECTION

In the article, "Studies in Immunity: V. Effect of Acute Diseases on the Reaction of the Skin to Tuberculin," by Drs. A. Graeme Mitchell, Waldo E. Nelson and Thomas J. LeBlanc in the March issue (AM. J. DIS. CHILD. **49**:695, 1935), "Cm." after "Rate" in the fourth and sixth columns of table 1 should be omitted.

Abstracts from Current Literature

Pathology, Bacteriology and Biochemistry

DISTRIBUTION OF THE IMMUNIZING ANTIGEN IN THE PNEUMOCOCCUS. LLOYD D. FELTON, J. Bact. **27**:90 (Jan.) 1934.

The author carried out the following study: Pneumococci, both type I and type II, were grown in the usual meat infusion broth, collected in a Sharples centrifuge, suspended over night in acetone at room temperature and dried in a vacuum desiccator. By various methods it was found possible to separate the constituents of the cell into fairly well defined fractions. The first division was into acid-soluble and acid-insoluble fractions. Only about 10 per cent of the immunizing activity of the cell remained in the acid-insoluble fraction. This immunity in white mice was largely heterologous. The acid-soluble fraction, on the other hand, contained most of the immunizing substances, and when this was injected into white mice type-specific immunity resulted. However, when this acid-soluble material was separated into alcohol-soluble and alcohol-insoluble fractions, these varied in immunizing activity. The acid alcohol-insoluble fraction produced type-specific immunity in a concentration of 10^{-8} Gm. (in white mice). Conversely, the acid alcohol-soluble fraction was less active and produced as well a certain degree of heterologous immunity.

STOESSER, Minneapolis.

THE AVAILABILITY OF IRON FROM DIFFERENT SOURCES FOR HEMOGLOBIN FORMATION. C. A. ELVEHJEM, E. B. HART and W. C. SHERMAN, J. Biol. Chem. **103**:61, 1933.

The availability of iron in different iron salts and in a few foods was determined by means of Hill's dipyridyl method and by animal feeding. It was found that the salts that reacted with dipyridyl supplied readily available iron for hemoglobin formation, while those not reacting (organic iron and iron in foods) showed slight availability, as determined by animal feeding. The value of various foods as a source of iron cannot be based entirely on their total iron content. The various forms of nonhematin iron, even insoluble salts, are much superior to the hematin compounds as a source of iron for the body. Ferric pyrophosphate is suggested as an available and agreeable iron preparation for clinical use. The dipyridyl method may be a valuable means of determining available iron in foodstuffs.

MCBRYDE, Durham, N. C.

THE EFFECT OF THE ANTERIOR LOBE PITUITARY, THE THYROID AND THE GONADS UPON PREADULT GROWTH. AUGUST A. WERNER, J. Missouri M. A. **30**:398 (Oct.) 1933.

The endocrine glands which affect pre-adult growth are the anterior lobe of the pituitary gland, the thyroid, the gonads, the pineal gland and the thymus. Those of major importance are the anterior lobe of the pituitary gland, the thyroid and the gonads. Disturbances of growth caused by the pineal gland are rare. Disturbancess due to dysfunction of the thymus are seen more frequently than those of pineal origin.

Pre-adult growth and sexual development are largely contingent on the time of output of certain hormonal secretions and the degree of function of the anterior lobe of the pituitary gland, the thyroid and the gonads.

The anterior lobe of the pituitary gland seemingly has more diverse functions than any of the other ductless glands. Among these are the production of the thyrotrophic hormone, the growth-stimulating hormones and the gonad-stimulating hormones. This gland has three types of cells: the chromophobe, eosinophil and

basophil. The former may later develop into the other two types. Tumors of this gland are usually not of the secretory type but rather of the pressure type.

The growth-stimulating hormone, as was shown by Cushing, is produced by the eosinophilic cells. In gigantism and acromegaly the gland shows a vast preponderance of these cells. Many investigators believe that the gonad-stimulating hormone is produced by the basophilic cells. Its action on growth is indirect, through the gonads which influence ossification and union of the epiphyses with the diaphysis.

If the secretion of the sex gland is delayed at the onset in the presence of growth hormone of the normal anterior lobe, the long bones, which have epiphyses, grow in excess of the bones of the torso, which have none.

If the growth-stimulating hormone of the anterior lobe is secreted at a rate greater than normal, yet not excessively, in the presence of normal onset of secretion and normal function of the gonads, there are resulting long extremities without a eunuchoid type of person.

If, under similar conditions, the secretion of the growth-stimulating hormone of the anterior lobe is excessive, gigantism results, usually with a eunuchoid type of person.

If the growth-stimulating hormone of the anterior lobe is secreted in excess after adult life is established, acromegaly is the result.

Failure of the anterior lobe of the pituitary gland to secrete sufficient growth-stimulating and sex-stimulating hormones in infancy, childhood and adolescence results in infantilism.

Cretinism is due to a congenital defect in, or destruction of, the thyroid gland. A child with this condition may grow in weight but not in height. Dentition is late. Mentality is decreased, at times even to imbecility. The body is dependent on the secretion of thyroxine to determine the rate of chemical interchange of all the body cells, thereby influencing metabolism and growth.

BERGER, Kansas City, Mo.

THE HYPOPHYSIS AND THE GROWTH OF THE ORGANISM. MAX ARON, Rev. franç. de puériculture **1**:205 (Sept.) 1933.

The anterior pituitary lobe secretes one hormone which stimulates the thyroid and one which excites the genital endocrine glands, and there seems to be one which influences growth. Whether there is a pituitary hormone which affects growth directly has not been determined, but it seems probable that the effect of the pituitary gland on growth can be explained by its indirect action through the thyroid and genital glands. Growth is determined primarily by the hereditary characteristics of the organism; it is influenced and coordinated by the hormones of the thyroid and genital glands and, possibly, other glands. The hypophyseal hormones regulate, and are in turn controlled by, the products of the other endocrine glands.

CRANE, Chicago.

INFLUENCE OF INSULIN ON BLOOD CALCIUM PARTITIONED BY MEANS OF ULTRAFILTRATION. A. CABITTO, Riv. di clin. pediat. **31**:1343 (Nov.) 1933.

The blood calcium is divided into ionized and colloidal calcium. Colloidal blood calcium is chemically combined with the blood proteins and cannot be dialyzed through a collodion membrane.

Dogs were used in these observations. Insulin was injected in doses varying from 1 to 2 units per kilogram of body weight. Forty minutes after each of the six injections the total calcium and the colloidal calcium in the blood were increased. The ionized calcium was increased with the larger doses of insulin, but was unchanged with the smaller doses.

HIGGINS, Boston.

INFLUENCE OF THYROXIN ON THE BLOOD CALCIUM. C. Rosso, Riv. di clin. pediat. **31**:1351 (Nov.) 1933.

Dogs were given injections of from 0.15 to 0.30 mg. of thyroxin per kilogram of body weight. Twenty minutes later the blood calcium was found to have increased slightly, while forty minutes later it had fallen considerably below the level in the controls. The ionized calcium—that which was capable of dialysis through a collodion sac—had diminished after twenty minutes and was still lower after forty minutes. The colloidal calcium—that which was combined with protein—increased during the first twenty minutes and then fell to an amount less than that before the drug was given. It is likely that the diminution of ionized calcium resulted from combination of some of the ionized calcium with the blood protein.

HIGGINS, Boston.

EFFECT OF INHALATION OF CARBON DIOXIDE ON BLEEDING. JOSEF MAX, Arch. f. klin. Chir. **178**:170 (Nov.) 1933.

Guinea-pigs kept in an atmosphere of 5 per cent carbon dioxide for from three to five minutes were found to have a lowered bleeding and clotting time. Healthy men showed a similar lowering and also an increase in platelets. The bleeding and clotting time in cases of jaundice, in men and dogs both, was shortened by the inhalations. Max advises the inhalation of carbon dioxide as a clinical measure in both treatment and prophylaxis.

DAFFINEE, Boston.

Nutrition

STUDIES ON THE INFLUENCE OF EXERCISE ON THE DIGESTIVE WORK OF THE STOMACH: I. ITS EFFECT ON THE SECRETORY CYCLE. FRANCES A. HELLEBRANDT and SARA L. HOOPES, Am. J. Physiol. **107**:348 (Feb.) 1934.

Severe and exhausting exercise inhibited the initial secretory response, being associated with a hypo-acidity or anacidity lasting as long as one hour. The initial inhibition was at times superceded by transitory hyperacidity. Mild activity either increased the acidity or left the peak acidity unchanged. The study was made on a healthy student of physical education.

NOURSE, Cleveland.

STUDIES ON THE INFLUENCE OF EXERCISE ON THE DIGESTIVE WORK OF THE STOMACH: II. ITS EFFECT ON EMPTYING TIME. FRANCES A. HELLEBRANDT and RUBYE H. TAPPER, Am. J. Physiol. **107**:355 (Feb.) 1934.

Determination of the emptying time of the stomach was made by fluoroscopic examination. Mild exercise tends to hasten the final emptying time, especially if it follows immediately the ingestion of the meal. Violent and exhaustive exercise inhibits gastric peristalsis, but this may be followed by a period of augmented activity, so that the final emptying is not much altered.

NOURSE, Cleveland.

STUDIES ON THE INFLUENCE OF EXERCISE ON THE DIGESTIVE WORK OF THE STOMACH: III. ITS EFFECT ON THE RELATION BETWEEN SECRETORY AND MOTOR FUNCTION. FRANCES A. HELLEBRANDT and RUBYE H. TAPPER, Am. J. Physiol. **107**:364 (Feb.) 1934.

Simultaneous observations on gastric acidity and motility made under conditions of rest and muscular activity showed a striking parallelism in response. Variations in the rate of evacuation must therefore be considered in any explanation of the changes in acidity observed. The findings suggest that the mechanisms controlling the change in secretion and motility in response to a meal must be identical.

NOURSE, Cleveland.

STUDIES ON THE INFLUENCE OF EXERCISE ON THE DIGESTIVE WORK OF THE STOMACH: IV. ITS RELATION TO THE PHYSIO-CHEMICAL CHANGES IN THE BLOOD. FRANCES A. HELLEBRANDT, HARRY D. BAERNSTEIN and SARA L. HOOPES, Am. J. Physiol. **107**:370 (Feb.) 1934.

No relationship was found between chemical changes in the blood and the composition of the gastric juice.

NOURSE, Cleveland.

MINERAL METABOLISM. JOSEPH C. AUB, Bull. New York Acad. Med. **10**:82 (Feb.) 1934.

The inorganic salts are composed of acid and basic radicles in a systematic and coordinated balance; their function is to maintain the p_H and osmotic pressure of the tissue fluids. An excessive intake of either is, under normal conditions, eliminated by the kidneys. The normal level varies between 150 and 160 milli-equivalents, with water and salts fluctuating together. When excess base is lost by excretion in disease, water is also lost, and dehydration results. When base is retained, edema occurs. Outside the cell, sodium is the predominating base, while potassium predominates inside the cell. Thus, when fluids are lost from the body, it is largely sodium which is excreted. When the body cells are broken down, there is a depletion of potassium salts (starvation).

In pyloric obstruction the fluid lost is largely hydrochloric acid. This loss cannot be replenished by intake of food (because of vomiting), and there is a definite tendency to alkalosis and gastric tetany. The relative balance must be established by loss of base through the urine. There is a concomitant fall in base and chloride in the blood plasma, with a rapid onset of dehydration, diminished urinary output and retention of nitrogen.

In the edema of nephrosis the inorganic salts are seriously involved, for when there is retention of water there is also retention of sodium and chloride. However, retention of salts is not invariably the result of damage to the kidneys. This is seen in chronic nephritis, in which there are large quantities of urine, with sodium and chloride washed from the body.

In metabolism of bone, phosphates are fully as important as calcium, though their importance is less stressed. These two elements are unique in the metabolic economy because they are continuously going in and out of the bones and are continuously being excreted, even in starvation. A change of calcium in the blood is reflected in the muscle tone. Low blood calcium is associated with neuromuscular irritability (tetany). High blood calcium leads to low muscle tone, increased excretion of calcium and changes in the bones and kidneys. The absorption of calcium is a complicated physiologic mechanism. Adequate absorption depends on proper digestion of fat and a proper supply of vitamin D. The chief storehouse for calcium is the trabecular system in bone near the epiphyses. Calcium metabolism is dependent not only on foods and vitamins but also on internal secretions (parathyroid and thyroid).

JAHR, Omaha.

A SKIN MANIFESTATION FROM THE EXCESSIVE ADMINISTRATION OF VITAMINS. F. F. PFISTER, J. A. M. A. **102**:533 (Feb. 17) 1934.

Pfister reports two cases which he believes indicate that excessive administration of vitamin-containing substances may produce cutaneous manifestations. The rash described is a fine papular one superimposed on an erythematous base and looking much like early weeping eczema. Large doses of haliver oil or viosterol had been administered. When these substances were withheld from the diet the lesions disappeared.

BONAR, Salt Lake City.

STUDIES OF VITAMIN G (B_2): I. YEAST AND LIVER PREPARATIONS AS A SOURCE OF VITAMIN G (B_2). RICHARD J. BLOCK and LUCILLE R. FARQUHAR, J. Biol. Chem. **103**:643, 1933.

The vitamin G content of various yeast and liver concentrates was determined by feeding experiments on albino rats. An average gain in weight of from 4.5 to 6 Gm. per day was made when the animals were fed liver concentrate no. 343

(Lilly) or yeast concentrate. There was no decrease in the vitamin G potency of these preparations after autolysis, digestion, treatment with alkali in the cold or prolonged heating after previous drying.

Liver concentrates prepared by Lederle and Chappell contained little, if any, vitamin G, notwithstanding their high content of the pernicious anemia factor.

McBryde, Durham, N. C.

Observations upon the Calcium and Phosphorus Metabolism in Certain Diseases of Bone. Walter de M. Scriver and Eleanor M. Venning, J. Clin. Investigation **13**:139 (Jan.) 1934.

In four cases of Paget's disease, one of solitary bone cyst and one of sarcoma of bone, the calcium and phosphorus metabolism was found to be within normal limits. No chemical evidence was found to link these conditions with parathyroid dysfunction. These studies and an analysis of the literature indicated that an intake of calcium of at least 1 Gm. daily is necessary to keep the calcium balance of patients with these conditions positive.

Guest, Cincinnati.

The Distribution of Blood Phosphorus After Suppression of Renal Function. Alta Ashley and George M. Guest, J. Clin. Investigation **13**:219 (March) 1934.

Studies of the distribution of phosphorus and other constituents of the blood were made in rabbits and dogs subjected to three experimental procedures (intravenous injections of diphtheria toxin and of trichloride of mercury and bilateral ligation of the ureters), which resulted in acute suppression of renal function. The principal changes demonstrated in the blood were: (1) an increase in inorganic phosphates, which was greater in the plasma than in the cells; (2) an increase in organic acid-soluble phosphorus (ester P) in the cells; (3) a decrease in chloride in both the plasma and the cells, and (4) an increase in nonprotein nitrogen. The observations were cited as further evidence supporting a hypothesis, previously offered, that a reciprocal relationship exists between chloride and phosphoric esters as anions in the cells, and that an interchange between the inorganic phosphates of the plasma and the ester P of the cells may serve an important function in adjustments of the acid-base balance of the whole blood.

Guest, Cincinnati.

Nutrition of the Normal Infant. Julian D. Boyd, J. Pediat. **4**:263 (Feb.) 1934.

In this critical review Boyd discusses the recent contributions to the literature concerning the feeding of normal infants, experimental data having a bearing on this subject and the results of a questionnaire sent to more than one hundred outstanding pediatricians in this country. Among the topics considered are, chiefly: the advantages and disadvantages of human breast milk, the value of minerals in the diet, the use of sweet and acidified cow's milk and of evaporated and dried cow's milk and the use and value of egg yolk, cereals, vegetables, fruits, cod liver oil and orange juice.

LeMaster, Evanston, Ill.

The Influence of Liver Degeneration and Recuperation on the Acid-Base Equilibrium of the Blood. W. D. MacNider, J. Pharmacol. & Exper. Therap. **50**:108 (Jan.) 1934.

Dogs intoxicated with ethyl alcohol for from six to twelve hours showed definite injury to the liver which was characterized by cloudy swelling, edema, vacuolation and, rarely, necrosis of liver cells. There was also injury to liver function, as was shown by the phenoltetrachlorphthalein test. The kidneys were not appreciably damaged. The alkali reserve of the blood was decreased. The animals that recovered showed return to normal of liver structure and function and of the alkali reserve.

Pilcher, Cleveland.

VITAMIN A IN MILK. W. C. RUSSELL, New Jersey Agric. Exper. Stat. Rec. **15**:70 and 522, 1933.

Less than 5 per cent of the vitamin A in the amount of dried alfalfa and corn silage usually fed appears in the milk of dairy cattle. For this reason it does not seem that increasing the amount of alfalfa and silage in the ration would increase the vitamin A content of the milk. When carotene is converted into vitamin A by the cow it appears in the milk in a colorless form. However, some of the carotene passes into the milk unchanged and is largely responsible for the color of the milk.

KUGELMASS, New York.

THE RELATION OF UPPER RESPIRATORY INFECTION TO NUTRITION IN INFANTS AND CHILDREN. MARSHALL CARLETON PEASE, New York State J. Med. **34**:146 (Feb. 15) 1934.

While not all nutritional disturbances of children are due to some focus of infection, it is difficult to underestimate the importance of such foci. This is especially true in paranasal sinusitis. Infections of the upper respiratory tract may produce diarrhea, vomiting, dehydration and acidosis. Primary infections of the nose may spread into all the sinuses and into the ear. Mastoiditis may give few signs, and roentgenograms should not be relied on in making the final diagnosis. Early operative treatment of mastoid and sinus infections is necessary. Concentrated fish liver oils "offer an immediate preventive measure of real importance."

AIKMAN, Rochester, N. Y.

THE EXPLOITATION OF VITAMIN A. S. W. CLAUSEN, New York State J. Med. **34**:154 (Feb. 15) 1934.

Deficiency of vitamin A in animals may lead to decreased resistance to infection. This has led to the belief that susceptibility to infections of human beings may be due to the use of food that is deficient in vitamin A, although no clinical signs of such deficiency may be present. The claims that concentrated vitamin A or its precursor carotene should be given to prevent infections need to be more carefully checked. A study of the plasma carotinoids in 1,322 children over 2 years of age was made. The plasma carotinoids show a distinct fall in infections; this fall does not precede the infection but results from it, and is probably due to decreased intake of food. The study shows that in not more than 5 per cent of the children were low carotinoids a factor in the production of infection. "By simple calculation it can be shown that high carotinoids are associated with increase of susceptibility in 1.2 per cent of the healthy children, in 0.9 per cent of those with mild infection, and in 8.1 per cent of those with severe infection."

Carotene was given to sixty-three patients with scarlet fever, without benefit and with no reduction in the number of complications. Clausen believes that the value of carotene as a preventive measure against infections has been much overestimated.

AIKMAN, Rochester, N. Y.

AN ENGLISH CASE OF PELLAGRA. LESLIE COLE, Brit. J. Child. Dis. **30**:262 (Oct.-Dec.) 1933.

An 8 year old girl showed a brownish scaly rash on the hands and later on the cheeks, associated with diarrhea, which appeared in early summer. There were six other children in the family; these appeared healthy.

The child's diet had been deficient in eggs, meat, fresh fruit and vegetables. In the hospital she was given a liberal diet and also autolyzed yeast (B_2), a preparation containing vitamins A and D and cod liver oil. After five weeks her general condition was greatly improved and there was only slight scaliness of the hands. However, after returning home she had more attacks of diarrhea, became increasingly listless and died. Permission for a postmortem examination was not obtained.

LANGMANN, New York.

CALCIUM AND PHOSPHORUS METABOLISM IN DISEASES OF THE THYREOPARATHYREOID APPARATUS: I. CALCIUM, PHOSPHORUS AND TOTAL METABOLISM IN HYPERTHYREOIDISM, AND THE PART PLAYED BY THE PARATHYREOID GLANDS. F. S. HANSMAN and F. H. WILSON, M. J. Australia **1**:37 (Jan. 13) 1934.

Hansman and Wilson believe that the evidence presented by Aub and his co-workers is not sufficient to justify the opinion that the negative calcium and phosphorus balance frequently found in hyperthyroidism is due to a specific effect on bone of the excess of circulating thyroxine. An analysis of their own experimental data obtained from a study of seven patients suffering from hyperthyroidism provides, they believe, definite evidence that associated hyperparathyroidism is the direct cause of the excessive mobilization and excretion of calcium and phosphorus in such cases. Their final conclusion is based on the following facts: (1) Three patients with hyperthyroidism who were treated with iodine manifested marked clinical improvement without a corresponding improvement in the calcium and phosphorus balance. (2) Four other patients with this condition who were treated with the roentgen rays showed marked change from a negative to a positive calcium balance without influence on the hyperthyroid state; this was thought to be due to the effect of the roentgen rays on the parathyroid glands. (3) Two patients with severe hyperthyroidism and associated hypoparathyroidism were found to maintain a positive calcium and phosphorus balance. (4) Though hyperthyroidism is frequently accompanied by a negative calcium and phosphorus balance, this is not invariably so. (5) Loss of calcium in hyperthyroidism has no special features to distinguish it from similar losses in other pathologic conditions associated with a negative calcium balance. In this work Hansman and Wilson were also unable to confirm the findings of others that the mobilized calcium is excreted predominantly in the feces.

GONCE, Madison, Wis.

CALCIUM AND PHOSPHORUS METABOLISM IN DISEASES OF THE THYREOPARATHYREOID APPARATUS: II. THE PROBLEM OF THE MODE OF ACTION OF VITAMIN D. F. S. HANSMAN, M. J. Australia **1**:81 (Jan. 20) 1934.

A summary of recent work on vitamin D in the treatment of hypoparathyroidism is given. From this it appears that there is no universal opinion on the relation of vitamin D to the parathyroid glands in hypoparathyroidism. Detailed metabolic studies were made by Hansman on two patients with hypoparathyroidism (associated with hyperthyroidism), who were treated with vitamin D. He concludes that the beneficial effect of vitamin D in hypoparathyroidism is not due to better absorption of calcium from the intestinal tract, to changes in the serum level of calcium, inorganic phosphorus or the calcium-phosphorus product, and suggests that vitamin D acts by making calcium available for tissue metabolism.

GONCE, Madison, Wis.

HOW DO VITAMINS ACT? ATTEMPT AT A UNIFORM INTERPRETATION. W. KOLLATH, Bull. Soc. scient. d'hyg. aliment. **22**:43, 1933.

Kollath considers that a deficiency disease results from both specific and nonspecific causes. The deficiency diseases which he places in the aplastic-consumptive group are characterized by the cessation of all cellular neoformation. In a second group (paraplastic-productive forms) consumption is reduced in a nonspecific manner. In this way it can be seen that beriberi is due not to deficiency of vitamin B_1 but to the presence of vitamin B_2 alone. Similarly, for rickets to appear, not only deficiency of vitamin B_2, but also the presence of a series of other substances, is necessary. Vitamins also play a part in resorption and elimination; they also act on the oxidation-reduction potential, which they accelerate (vitamin C) or inhibit (vitamins B_1 and B_2).

KUGELMASS, New York.

VARIATION OF THE MINERAL ELEMENTS OF THE BLOOD AS INFLUENCED BY IRRADIATION WITH LIMITED RAYS. S. MALCZYNSKI, Compt. rend. Soc. de biol. **112**:928 (March 10) 1933.

In these experiments, except for an interval of fifteen minutes, the following results were obtained.

The calcium and potassium were increased, the rise in calcium being the more sustained. There was a momentary increase in sodium, followed by a slight decrease. There was very little, if any, change in phosphorus.

WAHL, Cleveland.

SUMMER DIARRHEA AMONG THE INFANTS OF TURKESTAN. R. GUERSCHENOWITSCH, Nourrisson **22**:12 (Jan.) 1934.

In addition to the types of diarrhea encountered among infants in Turkestan, viz., simple, choleriform and dysenteric, two other forms are described: (1) an oligotoxic form, which fits in between the simple and the choleriform, and (2) a fermentative type, which is more common in children between 2 and 3 years of age. As in the United States, the breast fed infant has the best chance of escaping all the forms.

The summers in Turkestan are very hot, the temperature ranging from 40 to 50 C. (104 to 122 F.) in the shade and from 60 to 65 C. (140 to 149 F.) in the sun.

MCCLELLAND, Cleveland.

INDICATIONS FOR GAVAGE. B. WEILL-HALLÉ and MARCUS, Nourrisson **22**:90 (March) 1934.

According to Weill-Hallé and Marcus, gavage is indicated in the following conditions: (1) in cerebral injury or disease in infants which interferes with the physiology of sucking or swallowing, (2) in the trismus of tetanus of the new-born, (3) in diphtheritic paralysis affecting the soft palate, pharynx, larynx and esophagus, (4) in vomiting due to hyperactive pharyngeal reflexes, (5) in congenital malformations of the lips, jaws, tongue or palate, (6) in anorexia in infants suffering from severe or prolonged acute infections, (7) in prematurity and congenital debility and (8) in hypothrepsia in infants.

MCCLELLAND, Cleveland.

RESISTANCE OF RATS TO RICKETS-PRODUCING DIETS AND ITS IMPORTANCE. LUIGI BUTTURINI, Boll. d. Soc. ital. di biol. sper. **8**:1742, 1933.

The method for evaluating the antirachitic power of substances in rats is open to serious errors, because a fairly large percentage of the rats fail to develop rickets. Until the factors which interfere with the uniform development of experimental rickets in rats are known, the method of choice should be the curative one.

KUGELMASS, New York.

INFLUENCE OF ULTRAVIOLET IRRADIATION ON THE MAGNESIUM CONTENT OF THE BLOOD. A. CABITTO and C. ROSSO, Clin. pediat. **16**:1 (Jan.) 1934.

Having previously studied the effect of ultraviolet irradiation on blood calcium and potassium, Cabitto and Rosso now report the effect of such irradiation on the blood magnesium of dogs. After each exposure the magnesium falls, until it reaches a sustained low level after a course of exposures. This is attributed to diminution of cellular metabolic activity. The possibility of alterations in the mineral constituents of the blood should be borne in mind in the indiscriminate use of ultraviolet therapy.

DOOLEY, Kent, Conn.

NUTRITION OF THE INFANT. RAMÓN GARCIÁ MONTENEGRO, Arch. de med. inf. **3**:582 (March) 1934.

All children should be breast fed to comply with nature's laws. It is the duty of the physician to point out to the mother the necessity of nursing her child.

Any mother refusing to give her child the breast exposes it to a 60 per cent chance of death. In case the child cannot be nursed, cow's milk can be used, when modified, in most cases. At the age of from 6 to 8 months other foodstuffs, such as cereals, should be included in the diet.

SANFORD, Chicago.

INCREASE OF VITAMIN D IN YEAST BY ULTRAVIOLET IRRADIATION. S. N. MATZKO, Arch. tierernahr. Tierzucht **9**:623, 1933.

The vitamin D content of baker's yeast can be raised to from 5,000 to 10,000 units per gram by irradiation. When prepared in the presence of atmospheric oxygen and carbon dioxide, the material has no toxic action if administered in customary amounts. The vitamin potency remained unchanged during storage for two months, but weakened somewhat after four months.

KUGELMASS, New York.

COLLECTION OF HUMAN MILK IN ERFURT IN THE LAST SIX YEARS. M. E. KAYSER, München. med. Wchnschr. **80**:1893 (Dec. 1) 1933.

An average of fifty mothers contributed breast milk daily at the milk station in Erfurt. Between 1,900 and 3,100 liters of milk were collected annually. The mothers received an average income of from 30 to 40 marks a month for their milk. The milk is sterilized in 200 Gm. flasks. From the clinical reports of the hospitals using the milk there was no evidence of destruction of the vitamins.

BRAHDY, Mount Vernon, N. Y.

THE INFLUENCE OF ENVIRONMENT OF FAT IN THE TISSUE OF PIGS. J. E. BORMANN, Polish Agric. Forest. Ann. **30**:401, 1933.

In an investigation of the effect of feeding twice the quantity of rape oil ordinarily present in the fodder used, the temperature of the environment was found to affect the percentage of fat in the tissues, the saponification number and also the amount of fatty acids insoluble in water present in the fat of sows given rape oil and fed normally.

KUGELMASS, New York.

INFLUENCE OF PROLONGED CARBOHYDRATE FEEDING ON THE ACTIVITY OF THE HIGHER NERVOUS SYSTEM IN THE DOG. V. S. BRANDHENDLER and V. A. MUZUIKANTOV, Ark. biol. nauk **33**:81, 1933.

Prolonged feeding of meat and carbohydrate, along with the use of a dry bread powder as an unconditional stimulating agent, provokes a series of regular changes in the conditioned reflex activity of dogs. A carbohydrate diet used after a mixed diet produces at first a brief increase in all the conditioned and unconditioned reflexes. This is followed by a more lasting decrease in both and by absolute differentiating inhibition. A carbohydrate diet given after a meat diet induces a fall in the conditioned reflexes, followed by a leveling and a constant fall in the unconditioned reflexes. A meat diet following a carbohydrate diet causes a brief but sharp fall in both the conditioned and the unconditioned reflexes, followed by a prolonged rise in both and by removal of the differentiating inhibitions.

KUGELMASS, New York.

THE PRESENCE OF THE ANTI-SCURVY VITAMIN IN VARIOUS FRUITS AND VEGETABLES. N. N. IVANOV, V. N. BUKIN, B. O. BOROKHOVICH and K. L. POVOLOTZKAYA, Bull. App. Bot. (Genetics Plant Breeding [U. S. S. R.]), ser. A, no. 8, 1933, p. 95.

The basal diet given to guinea-pigs in testing strawberries and currants for vitamin C consisted of the following: oats, 86 Gm.; bran, 10 Gm.; yeast, 4 Gm., and egg yolk, 7.5 Gm. Wild strawberries were somewhat inferior to cultivated varieties in their antiscorbutic properties. Among the four varieties of black currants the effective quantity ranged from 1 to 12 Gm. After these experiments

the diet was changed to one of oats and autoclaved hay. Results were negative with three varieties of grapes. Of eleven varieties of apples "Antonovka" had the highest potency; 3 Gm. was sufficient to prevent scurvy. Cranberries were also efficient. Freezing the berries at —8 C. did not decrease their antiscorbutic action. Cabbage grown in the more arid region of the steppes contained more vitamin C than cabbage grown in the northern regions. Kohlrabi is high in vitamin C.

KUGELMASS, New York.

INFLUENCE OF CERTAIN HORMONES ON CARBOHYDRATE-PHOSPHATE METABOLISM. A. MANOILOVA, N. UTOCHNIKOVA and A. GORDON, Russk. j. physiol. **14**:309, 1931.

The intimate relation between carbohydrates and phosphorus compound in the organism is emphasized by the fact that hormones such as insulin and epinephrine, which influence carbohydrate metabolism, produce a change in the content of inorganic phosphorus in the blood parallel with the change in the sugar content. Insulin lowers the inorganic phosphorus by promoting its conversion into the organic phosphorus compound lactacidogen. Epinephrine at first raises the inorganic phosphorus content of the blood by furthering the decomposition of lactacidogen. The effects of pituitary in this direction are negligible. Diverse results are due to the fact that the change in the blood phosphorus often follows a rhythmic course, and that the inorganic phosphorus has not always been determined at regular intervals after the introduction of the hormone.

KUGELMASS, New York.

ANALYSIS OF PYLORIC SECRETION. M. G. NIKOLAEVA, Russk. j. physiol. **16**:199, 1933.

Section of the splanchnic nerves in dogs with an isolated pylorus increased the secretion of gastric juice, but did not alter the percentage of increase brought about by hydrochloric acid. The effect of irrigation of the mucous membranes by solutions of various salts and drugs is recorded.

KUGELMASS, New York.

COW'S MILK IN MANCHURIA AND MONGOLIA: III. PHOSPHORUS CONTENT OF COW'S MILK AND ITS DISTRIBUTION. M. SUGIURA, J. Orient. Med. **21**:1 (July) 1934.

Sugiura examined the quantitative distribution of the phosphorus fraction in cow's milk, with the following results: The total phosphorus was found to be 89.53 mg. per hundred cubic centimeters; phosphatide phosphorus, 3.95 mg.; casein phosphorus, 14.89 mg.; acid-insoluble phosphorus, 18.84 mg.; inorganic phosphorus, 54.07 mg.; organic phosphorus, 16.67 mg., and acid-soluble phosphorus, 70.69 mg.

EDITOR'S SUMMARY.

CHEMICAL DIFFERENCES BETWEEN MALE AND FEMALE. G. JOACHIMOGLU and K. LOGARA, Praktika (Akad. Athenon) **8**:16, 1933.

Rickets is rare in Greece because of abundant sunlight, but deficiency in vitamin A due to types of food is common. A form of idiopathic day blindness caused by xerosis is epidemic in nature. Foods rich in vitamin A cure the condition, which occurs principally in men. In women it is due to age and changes in the generative organs. Women are less susceptible to the disorder because of the storage of vitamin A in the fatty tissues. Poulsson demonstrated that cow fat contained more vitamin A than bull fat. The incidence of the avitaminotic disturbance in males and females is shown graphically, at ages from birth to 80 years.

KUGELMASS, New York.

INFLUENCE OF THE INTAKE OF CITRIC ACID ON THE CITRIC ACID OF THE BLOOD. T. THUNBERG, Acta path. et microbiol. Scandinav. (supp.) **16**:535, 1933.

The citric acid content of the blood was raised by ingestion of citric acid from 27.6 to 38.2 mg. per liter of serum in one healthy man, from 16.5 to 28.5 mg.

in a woman and from 32.6 to 60.2 mg. in a man with acute hepatitis. In a man with a low citric acid content of the blood a rise of only from 17.4 to 26.1 mg. per liter of serum occurred after ingestion of the acid. The normal citric acid content of the blood is 25 mg. per liter of serum. A "citric dehydrogenase" found in cucumber seed was used for estimating the citric acid (Thunberg's method).

KUGELMASS, New York.

INFANTILE SCURVY TREATED WITH ASCORBIC ACID. E. SVENSGAARD, Hospitalstid. **77**:187 (Feb. 13) 1934.

Svensgaard reports two cases of advanced scurvy, with complete recovery after a few days' treatment with ascorbic acid. There was no addition of natural vitamin C to the diet.

ELGHAMMER, Chicago.

LESIONS DUE TO COD LIVER OIL AND THEIR TENDENCY TO HEAL. H. ANDERSSON, Upsala läkaref. förh. **39**:17 (Dec.) 1933.

Andersson followed the development and the healing of the lesions produced in white mice by giving 3 cc. of cod liver oil per kilogram of body weight daily. Pigmental and vacuolar degeneration, transformation of muscle cells into connective tissue and sometimes degenerative fatty infiltration and calcareous incrustation were seen in the heart. Conglomeration and pigmental degeneration of the cells of the medulla appeared in the suprarenals; parenchymatous degeneration and calcareous incrustation were sometimes present in the kidneys, and pigmental degeneration and sometimes stasis and degenerative fatty infiltration and, in four cases, necrosis, in the liver. The lesions usually appeared independently of the diet, but developed more rapidly with an incomplete diet. Some lesions healed well; healing of pigmental degeneration, calcic incrustation and degenerative fatty infiltration was not observed. There was never complete restitution.

ELGHAMMER, Chicago.

IMPORTANCE OF DIET FOR REGENERATION OF INJURIES TO HEART MUSCLE DUE TO COD LIVER OIL. E. AGDUHR, Upsala läkaref. förh. **39**:65 (Dec.) 1933.

Agduhr's electrocardiographic and histologic studies in white mice with cardiac lesions produced by treatment with cod liver oil seem to him to show that regeneration and restitution of the muscle cells of the heart occur more readily if a complete diet is given during the period of healing. The results of healing are especially notable if an incomplete diet is given during the time of treatment with cod liver oil and a complete diet after the end of the treatment.

ELGHAMMER, Chicago.

Prenatal Conditions

A CASE OF MALFORMATION ASSUMED TO BE TRUE HERMAPHRODITISM. JOSEPH MCFARLAND, Am. J. Path. **9**:549 (Sept.) 1933.

A mass of tissue which contained testicular and epididymal tubules, but no interstitial cells, was removed from a femoral hernia in a middle-aged otherwise perfectly formed woman. The author considers the case one of true hermaphroditism.

MOORE, New York.

CONGENITAL HEART DISEASE WITH PULMONARY ARTERITIS; INTERVENTRICULAR SEPTAL DEFECT, DEXTROPOSITION OF THE AORTA AND DILATATION OF THE PULMONARY ARTERY. HAROLD L. STEWART and BAXTER L. CRAWFORD, Am. J. Path. **9**:637 (Sept.) 1933.

The clinical, anatomic and histologic features of a case of sclerosis of the pulmonary artery and arteritis associated with an interventricular septal defect, dextroposition of the aorta and dilatation of the pulmonary artery are presented

and discussed. There were no symptoms until the last few months of life, and death occurred at the age of 60—the highest age ever attained by a person with this combination of congenital lesions. The shunt through the defect in the ventricular septum was probably arteriovenous; this permitted the combined force of both ventricles to unite in overcoming the resistance offered by the sclerotic lesser circuit. The evidence adduced, although not empirical, strongly favors a syphilitic origin for the lesions in the pulmonary artery, the pulmonary parenchyma, the pleura and the bronchi.

AUTHORS' ABSTRACT.

CONGENITAL ARTERIOVENOUS COMMUNICATION. F. G. LINDEMULDER, Am. J. Roentgenol. **28**:481 (Oct.) 1932.

Congenital arteriovenous communication is rare and may be situated in various parts of the vascular system. To date about fifty cases have been reported. Of the two cases reported by Lindemulder one demonstrated that in encephalography the enlarged ventricle is on the side of the lesion and the deviation of the brain is toward the side of the arteriovenous communication (left cerebral cortex). This finding is opposite to that previously described in ventriculography. The second case is one in which there was hypertrophy of an extremity, this variation being demonstrated in the roentgen studies of both hands.

STULIK, Chicago.

MULTIPLE CONGENITAL RIB AND SPINAL DEFORMITIES. JOSEPH H. SHAIN, J. Pediat. **3**:870 (Dec.) 1933.

The literature on deformities of the ribs and vertebrae is briefly reviewed. Among the anomalies of the ribs are: cervical ribs, variations in size and shape, bifurcation, fusion, lumbar ribs and total absence of one or more ribs. The congenital anomalies of the spine mentioned by the author include: spina bifida occulta, variations in the bodies of the vertebrae, defects in the laminae, congenital anomalies of the cervical spine, numerical variations in the thoracolumbar region, sacralization and deformities in the low lumbar, sacral and coccygeal regions. The case of a boy showing numerous anomalies of the ribs and spine is reported.

LEMASTER, Evanston, Ill.

CONGENITAL CYSTIC DISEASE OF THE LUNGS. D. H. COLLINS, J. Path. & Bact. **37**:123, 1933.

A case of congenital cystic disease of both lungs is described with a peculiar giant cell hyperplasia of unknown cause in all the lymph nodes.

[ARCH. PATH.]

SOME RENAL ABNORMALITIES. O. L. ADDISON, Proc. Roy. Soc. Med. **27**:407 (Feb.) 1934.

Congenital abnormalities of the genito-urinary tract are extremely common and are the most frequent of all congenital abnormalities. Many are unimportant and give rise to no symptoms, but a large proportion lead to serious ill health or death at an early age. Ectopic, single, horseshoe and double kidneys are not infrequent. The last two conditions are especially liable to lead to hydronephrosis. Double ureters on one or both sides are not uncommon. Hydronephrosis due to congenital abnormalities is seen in three forms: (1) the closed type, (2) the intermittent type and (3) the open type, which is associated with megalo-ureter and is frequently bilateral. The three types are described.

WILLIAMSON, New Orleans.

EXPERIMENTAL PRODUCTION OF CYCLOPEAN CHICKS. E. WOLFF, Compt. rend. Soc. de biol. **114**:1030, 1933.

Cyclopia occurs spontaneously in birds with extreme rarity. Embryologists have not succeeded in producing these monsters among amniotes (reptiles, birds

and mammals). However, by utilizing the local irradiation method of Ancel and Wolff, various types of cyclopia were obtained with considerable regularity, according to the period of development, the localization and the extent of the intervention. Sixty-three chicks with cyclopia were demonstrated, forty of which had lived more than ten days. Irradiation of the anterior end of the neural groove within from eighteen to twenty-two hours after incubation produced rudimentary, one-eyed median cyclopia. Irradiation of embryos beyond the two somite stage resulted in single orbit cyclopia, with the two eyes more or less developed.

J. E. Lebensohn, Chicago. [Arch. Ophth.]

Coarctation and Stenosis of the Aorta. R. Pereiras, R. Incián and R. P. de los Reyes, Arch. de med. inf. **2**:218 (April) 1933.

The authors report a case of this condition with observations at autopsy. Before autopsy the diagnosis of stenosis in the new-born was made, on account of the site and other abnormalities indicating a persisting foramen ovale. The authors stress that it is advisable not to use mercurial salts as diuretics and emphasize the importance of dextrose treatment in myocarditis.

Sanford, Chicago.

Spina Bifida. B. Sánchez, Arch. de med. inf. **2**:234 (April) 1933.

Spina bifida is one of the most frequent of congenital malformations. The etiology can best be understood by studying the embryology of the fetus. The treatment is surgical, when possible.

Sanford, Chicago.

Reduplication of the Right Auricle of the Heart; Unusual Changes in the Pulmonic Arteries Associated with Patent Foramen Ovale. H. Gombert, Beitr. z. path. Anat. u. z. allg. Path. **91**:483, 1933.

Reduplication of a cardiac atrium unassociated with other gross malformations of the heart is a rare anomaly. Gombert could collect only fifteen instances from the literature. In fourteen the left auricle was double; in only one other case was there reduplication of the right auricle similar to the condition described. Both cases occurred in adults, Gombert's patient being a woman, aged 42. The left auricle was enlarged, and its wall was hypertrophied. The right auricle appeared small externally. It consisted of two cavities, each the size of a walnut. The superior vena cava emptied into the middle auricle. The inferior vena cava opened into the lateral portion of the duplicated right auricle, but delivered most of its blood into the left auricle through a large foramen ovale. The two parts of the right auricle communicated with each other by a small opening through the septum that separated the two parts. The anomaly is ascribed to a failure of union of the primitive auricular septum. In another case, also in a woman, aged 42, an open foramen ovale and hypertrophied right side of the heart were associated with peculiar changes in the terminal branches of the pulmonic artery in the lungs. A proliferation of the endothelium at the point of division of the small arteries acted as a sort of valve. Beyond this point the vessel was tortuous and angioma-like. The condition is ascribed to the altered mechanics of the pulmonary circulation.

Schultz, Evanston, Ill. [Arch. Path.]

Congenital Deformity of the Spine. Horst Schmidt, Monatschr. f. Kinderh. **59**:241, 1934.

Schmidt gives a brief review of the literature on congenital deformities of the spine. He then reports the case of a 2 year old infant who was admitted to the clinic for paralysis of both legs. By roentgen examination it was found that the third thoracic vertebra was much smaller than the others. This defect was confirmed on postmortem examination, as the child died shortly after admission of

pneumonia. As the labor had been difficult, Schmidt admits the possibility of trauma as an etiologic factor, but he is convinced that there was a congenital defect in the vertebra.

GERSTLEY, Chicago.

STUDY OF VASCULAR ANOMALIES BY MEANS OF INJECTION AND ROENTGENOGRAPHY. A. HINTZE, Virchows Arch. f. path. Anat. **289**:705, 1933.

Reproductions of seven excellent roentgenograms support Hintze's thesis of the value of contrast injection and roentgenography in the study of vascular anomalies. The method is the subject of a more or less general discussion. Three cases are described illustrating the differences between the vascular anomalies of congenital malformations and benign tumors, in which the variation of the vascular tree is looked on as physiologic and harmonic, and the abnormalities of the circulatory system in the presence of malignant tumors.

SCHULTZ, Evanston, Ill. [ARCH. PATH.]

CONGENITAL INSUFFICIENCY OF THE TRICUSPID VALVE. H. GÖTZ, Virchows Arch. f. path. Anat. **291**:835, 1933.

The anomaly described was observed in the heart of a child who died at the age of 8 months. The insufficiency of the valve was due to downward misplacement of the medial and posterior segments; the shape of the latter was also abnormal. The anterior segment was normal in shape and position, but lacked cordae tendineae and papillary muscles and was broadly united to the wall of the ventricle. The medial segment was similarly devoid of cordae tendineae and papillary muscles. These structures were present in the posterior segment, but the latter was perforated at its middle. Endocardium was absent or incompletely developed in portions of the ventricle. It is to the defective development of the endocardium that the valvular anomaly is ascribed.

DOUBLE RECTUM IN A GIRL WITH A RECTOVAGINAL FISTULA. R. J. HARRENSTEIN, Nederl. tijdschr. v. geneesk. **77**:3669 (Aug. 12) 1933.

Harrenstein describes a case of double rectum in a girl aged 1½ years, in which he successfully removed the lower portion of the partition of both halves of the rectum and closed the fistula to make a normal structure. Microscopic examination of the removed section showed that it contained all the layers of the partition of the rectum twice. A summary is given of rare cases of this condition associated with partial doubling of the intestine, and special attention is paid to the doubling of the appendix.

VAN CREVELD, Amsterdam, The Netherlands.

ROENTGEN DIAGNOSIS IN CONGENITAL MALFORMATIONS. H. W. ELSHOVE, Nederl. tijdschr. v. geneesk. **78**:1216 (March 17) 1934.

Elshove describes a case in which the probable diagnosis of "anencephalic child in the uterus" could be verified by means of a roentgenogram. Positive sign of the death of the child could not be seen on the film. A review of the literature is given.

VAN CREVELD, Amsterdam, The Netherlands.

Diseases of the New-Born

THE OSSIFICATION IN THE EXTREMITIES OF THE NEW BORN. T. MENEES and L. E. HOLLY, Am. J. Roentgenol. **28**:389 (Sept.) 1932.

The upper and lower extremities were studied in six hundred and forty infants. The average sequence of appearance of centers of ossification were: (1) the lower part of the femur, (2) the upper part of the tibia, (3) the head of the humerus and the cuboid, (4) the coracoid, (5) the hamatum and capitatum, (6) the external cuneiform and (7) the part of the upper femur. In only eleven of thirty-one infants with a unilateral appearance of an epiphysis could this be traced sufficiently

to determine right-handedness or left-handedness. In nine of these eleven the side of preference and that of the early epiphysis agreed. Girls showed a higher percentage of epiphyses than boys. This was true in all sites except the upper part of the tibia, where the incidence was practically equal for both sexes. With increasing weight, length and menstrual age the percentage of epiphyses increases roughly, but not exactly in a parallel manner. The percentages for both sexes were: head of the humerus, 46.8; the coracoid, 12; the capitatum, 8.2; the hamatum, 7.8; the elbow, 0; the head of the femur, 0.6; the lower epiphysis of the femur, 99; the upper epiphysis of the tibia, 80.6; the cuboid, 45, and the third cuneiform, 2.

STULIK, Chicago.

BENIGN BONE CYST IN THE NEWBORN. VITO WITTING and JAMES B. GILLESPIE, Illinois M. J. **65**:451 (May) 1934.

Witting and Gillespie report a case of a benign cyst of the left fibula in a newborn infant. The diagnosis was made by histologic examination. The benign course and the roentgenographic appearance of the growth differentiated it from a so-called pseudarthrosis. It is a lesion entirely different from the three described in the literature as congenital bone cysts.

BARBOUR, Peoria, Ill.

PATHOLOGY OF ICTERUS. PAUL KLEMPERER, New York State J. Med. **33**:1309 (Nov. 15) 1933.

This review of icterus neonatorum and icterus gravis of the new-born is part of a symposium, "Some Disorders of Liver Function."

AIKMAN, Rochester, N. Y.

GENITOSUPRAPUBIC SCLEREDEMA OF THE NEW-BORN. G. BLECHMANN and S. MENARD, Bull. Soc. de pédiat. de Paris **31**:31 (Jan.) 1933.

A boy, 2 months old, showed an area of scleredema involving the skin of the suprapubic region and extending onto the inguinal folds. He had marked asphyxia at birth and mild jaundice of the new-born, which disappeared quickly. The condition did not seem to give the infant any discomfort. No explanation of the pathogenesis is attempted.

BENJAMIN, Montreal, Canada.

PROTEUS MENINGITIS IN THE NEW-BORN. JEAN CATHALA and P. GABRIEL, Bull. Soc. de pédiat. de Paris **31**:174 (April 25) 1933.

A girl, 17 days old, showed signs of meningitis. The spinal fluid, which was purulent, contained numerous micro-organisms and a markedly increased number of cells, mostly polymorphonuclear leukocytes. A pure growth of Bacillus proteus-vulgaris was obtained from every sample of spinal fluid. Tests on mice, guinea-pigs and rabbits showed that the organism possessed a high degree of pathogenicity for these animals.

BENJAMIN, Montreal, Canada.

ESTABLISHMENT OF THERMOREGULATION IN THE NEW-BORN. A. GINGLINGER, Rev. franç. de puériculture **1**:230 (Sept.) 1933.

Ginglinger's results in animal experimentation and results of other investigators who have studied heat production and dissemination in man indicate that the newborn infant behaves as regards heat production similarly to young homothermic animals which are endowed at birth with the means of chemical regulation of heat production but in which the physical mechanism which limits the dissemination of heat has not yet developed.

CRANE, Chicago.

SEPTIC FEVER IN THE NEW-BORN. S. FALCON, Arch. de med. inf. **2**:258 (April) 1933.

Septic fever comprises various types of fever in which no infectious process is involved, such as the fever subsequent to lesions of the nervous centers in obstetric

accidents, the transient fever of the new-born, the protein fever of Finkelstein, the salt fever of Meyer and the sugar fever of Moro. Other causes are the dry milk fever and the condensed milk fever described by the French authors, the prescorbutic fever, the fever observed after sudden changes of temperature and the so-called syndrome of the south wind, as described from Lyon. The most interesting point is its pathogenesis, which seems to be related to some disturbance of water metabolism.

SANFORD, Chicago.

TYPE, GENESIS AND INCIDENCE OF INJURIES OF THE EYE IN THE NEW-BORN. F. SCHENK, Med. Klin. **29**:1433 (Oct. 20) 1933.

In 27,100 deliveries of infants at the Universitäts-Frauenklinik in Praha, Czecho-Slovakia, injuries of the eye occurred only twenty-nine times, even when such minor injuries as marks caused by pressure of the forceps and excoriations are included. The more serious injuries were edema of the eyelids, subconjunctival hemorrhage, protrusion of the bulb, lagophthalmos and hemorrhages of the iris, but there were no instances of orbital fracture. Injury followed spontaneous labor eight times, Nägele's method of delivery fifteen times and delivery with Kielland's forceps six times. The means of delivery seemed to be less important in determining the incidence of ocular trauma than did the lapse of time between the rupture of the membranes and the birth of the child.

DOOLEY, Kent, Conn.

CONGENITAL LOCALIZED OSTEOMYELITIS OF THE SKULL. W. LADEWIG, Virchows Arch. f. path. Anat. **289**:395, 1933.

A child born five weeks prematurely died nineteen hours after a normal delivery. At birth a tumor-like elevation of the scalp was noted in the left parietal region. Necropsy showed this to be an area of localized osteomyelitis of the parietal bone, with abscess. The inflammatory process had extended to the scalp and to the dura, where it was productive. There had been considerable new formation of bone. Diplococci could be seen in sections of the lesion. The process is held to have been the result of transplacental hematogenous infection. No history of infection of the mother during her pregnancy could be obtained.

SCHULTZ, Evanston, Ill. [ARCH. PATH.]

RUPTURE OF LIVER IN THE NEW-BORN. EVA HOLMBERG, Finska läk.-sällsk. handl. **75**:1067 (Nov.) 1933.

In necropsies on more than one thousand fetuses observed in the General Lying-in Hospital in Helsingfors from 1924 to 1932 there were three cases of ruptured liver in fetuses born at full term, two of this condition in infants following spontaneous delivery, seven in premature infants and nine in fetuses weighing less than 1,000 Gm. Subcapsular hematoma of the liver was found in eleven fetuses born at full term and in twenty-six premature fetuses. The rupture of the liver is believed to be due to trauma, with asphyxia and presumably also a pathologic tendency to hemorrhage as disposing factors.

ELGHAMMER, Chicago.

Acute Infections

THE VALUE OF ANTITOXIN IN THE TREATMENT OF SCARLET FEVER. LAWRENCE A. KOHN and IZARD JOSEY, New York State J. Med. **33**:645 (May 15) 1933.

A study of two hundred and two cases of scarlet fever, all in adults or older children who were treated with an antitoxin prepared according to the method of Dochez by the New York State Department of Health is described. The antitoxin had a definite favorable effect, and while it did not reduce the incidence of complications, they were less severe.

AIKMAN, Rochester, N. Y.

SCARLET FEVER CONTROL. FRANK W. LAIDLAW, New York State J. Med. **33**:684 (June 1) 1933.

Laidlaw discusses the problems of the health officer in dealing with scarlet fever.

AIKMAN, Rochester, N. Y.

FATAL ACCIDENT FOLLOWING ADMINISTRATION OF DIPHTHERIA ANTITOXIN; DURATION OF PASSIVE IMMUNITY SHORTENED BY SERUM REACTION; SENSITIZATION BY INGESTION OF HORSE SERUM. PAUL VONDERWEIDT, Bull. Soc. de pédiat. de Paris **31**:63 (Jan.) 1933.

A girl, 7 years of age, showed a severe infection of the throat with Bacillus diphtheriae seven days after she had received an injection of 5,000 units of diphtheria antitoxin. This injection was followed by a severe serum reaction, despite the fact that she had never had any previous injection of horse serum; she had, however, taken horse serum by mouth about four to six weeks previously, and this had apparently sensitized her to horse serum. Seven days after the first injection of serum severe diphtheria involving both tonsils, the pharynx and the uvula developed. She was given an injection of 0.4 cc. of diphtheria antitoxin, followed within one to two hours by a second injection of 2 cc., and then a third injection of 60 cc. about one to two hours following the second dose. A severe serum reaction began soon after the last injection. This became progressively more alarming, and the child died twenty hours afterward. Repeated injections of ephedrine had no beneficial effect. It is believed that the serum sickness following the prophylactic injection of antitoxin hastened the excretion of the latter and thus shortened the duration of passive immunity.

BENJAMIN, Montreal, Canada.

TREATMENT OF MEASLES WITH AMIDOPYRINE. M. SCHACHTER and L. SCHWARTZ, Progrès méd., March 31, 1934, p. 549.

After several years' trial the authors are not convinced that amidopyrine has any specific value in the treatment of measles. In their locality (Budapest) measles is not an especially fatal disease, and perhaps their cases were not severe enough to show the results reported by some authors. Certainly the early administration of amidopyrine is vastly better than the classic early administration of a cathartic. In regard to alleviation of the rash, lowering of the temperature or effect on the complications amidopyrine has no particular value over other antipyretics.

SANFORD, Chicago.

UNUSUAL REACTION OF THE HEMATOPOIETIC SYSTEM FOLLOWING VACCINATION. R. CANINO, Pediatria **42**:631 (June 1) 1934.

The case of a child 18 months of age who a short time after vaccination (smallpox) showed secondary anemia, with early signs of metaplasia and relative agranulocytosis, is described.

SIGNORELLI, New Orleans.

GONOCOCCIC INFECTION IN INFANCY. J. M. PAEZ, Arch. de med. inf. **2**:249 (April) 1933.

This infection attacks children of any age. In a boy it almost never passes to the chronic stage, but heals soon, whereas in girls it almost always becomes chronic, occurring as vulvovaginitis sustained by mixed infections with other organisms. It must be treated for a long time, local antiseptics with vaccination and autovaccination being used. It attacks all the mucous membranes, but shows a preference for the genital apparatus, where it maintains better living conditions.

SANFORD, Chicago.

PARALYTIC COMPLICATIONS IN THE COURSE OF ANTIRABIC TREATMENT. L. MORQUIO, Arch. de pediat. d. Uruguay **4**:258 (July) 1933.

The author discusses in detail the efficacy and the possible complications of antirabic treatment. Two cases from the author's personal experience are reported, one illustrating the sequelae and the other the inadequacy of Pasteur's treatment in certain cases.

The first case is that of a boy, aged 5, in whom in the course of the antirabic treatment and shortly before its completion severe headache, rigidity of the neck, a positive Kernig's sign and complete facial palsy of the right side suddenly developed. The spinal fluid revealed a positive reaction to the Pandy test and slight lymphocytosis. All the symptoms subsided within a week, except the facial palsy, which disappeared within a year.

The second case was that of a boy, 7 years old, who was given a complete course of the classic Pasteur antirabic treatment, beginning two days after a dog bite. Fifty-five days after the last injection he showed the typical signs of rabies, together with a paralytic syndrome of the type of Landry's acute ascending paralysis. Postmortem examination confirmed the diagnosis of rabies.

In connection with the latter case the author discusses the differential diagnosis between true rabies and so-called "laboratory rabies" or the paralytic syndromes and hydrophobic manifestations which appear in some instances to be occasioned by the antirabic treatment. He believes that the main differential points are a shorter incubation period, less severe symptoms and a better prognosis in the "laboratory rabies" clinically and on postmortem examination absence of Negri bodies and negative results of the inoculation of rabbits. SCHLUTZ, Chicago.

RHINOPHARYNGEAL DIPHTHERIA IN A NEW-BORN INFANT WITH SEVERE CONGENITAL SYPHILIS. N. L. BLOISE, Arch. de pediat. d. Uruguay **4**:276 (July) 1933.

The author reports a case of rhinopharyngeal diphtheria in a new-born infant with congenital syphilis as confirmed by a strongly positive Wassermann reaction of the blood of both the baby and the mother. Intensive antisyphilitic treatment was started at birth, but on the fourth day sanguinopurulent coryza appeared without the early cutaneous manifestations of syphilis. A few days later an extensive gray, false membrane suggestive of diphtheria was noticed in the pharynx. Cultures from the nose and throat were negative for spirochetes but revealed an abundant growth of Klebs-Löffler bacillus. The culture from the mother's throat was likewise positive for the diphtheria bacillus. The baby died on the eleventh day of life, in spite of the intensive antisyphilitic and antidiphtheritic treatment.

The author points out the rarity of the condition and suggests that in all cases of coryza in syphilitic children resistant to the specific treatment nasal diphtheria should be ruled out. SCHLUTZ, Chicago.

PREVENTION OF AN EPIDEMIC OF MEASLES IN THE CASA NACIONAL DEL NIÑO. A. ARIZTIA, Rev. chilena de pediat. **4**:470 (Oct.) 1933.

In the section of the hospital containing older children four large epidemics occurred during the past year. Twenty-nine per cent of the population contracted measles. It is from this group that a large amount of convalescent serum was obtained. It was taken from children who had negative tuberculin reactions and who had had no severe complications with the attack of measles. The serum was withdrawn from seven to nine days after apyrexia. It was tested for the Wassermann reaction, carefully tested for bacterial contamination and then preserved by the addition of 0.5 per cent phenol. After a second bacteriologic control test it was ready for use. The serum was given the fourth or sixth day after incubation. Two or 3 cc. was given as an immunizing dose.

Infants under 3 months of age were not given the serum, as they do not seem to be susceptible to the infection. Ariztia found the protection effective in the very young infants. Either it prevented occurrence of the disease, or the disease appeared in a mild form. In contrast to the experience of former years, the mortality was very low.

The results were not as certain in the older children and the attending adults, but were striking enough to warrant the use of the convalescent serum as the best protection against the disease.

SCHLUTZ, Chicago.

AFFINITY OF DIPHTHERIA TOXIN FOR NERVOUS TISSUES. A. BACHMANN, Rev. Soc. argent. de biol. **9**:389 (Oct.) 1933.

Bachmann states that animals entirely immunized with antitoxin died when given an injection of diphtheria toxin directly into the cerebrum, while control animals, which received a subcutaneous injection, could stand much larger doses of toxin. Following previous studies on the affinity of the diphtheria toxin for the nerve tissues, the author made experiments to observe the effect of the L+ mixture when injected into the brain. The animals showed a picture of intoxication following a minimum lethal dose of toxin. The author believes that death was caused by the toxin and not by the physiologic serum used in the injection. This belief is especially supported by the fact that the lethal action of the mixture of toxin-antitoxin can be neutralized by increasing the dosage of antitoxin and that animals do not die following the cerebral injection of this neutralized mixture.

THERAPEUTIC ACTIVITY OF VACCINIA IMMUNE SERUM. K. VOM HOFE and W. KRANTZ, Med. Klin. **29**:1366 (Oct. 6) 1933.

Knowing that a mixture of the virus and the immune serum fails to cause vaccinia when inoculated into the cornea of the rabbit, these investigators studied the effect of immune serum intravenously injected at varying times, from five hours to four days after corneal inoculation with vaccinia virus, and were able to arrest the infection. The immune serum was obtained from rabbits which had been inoculated in the cornea from three to four weeks before.

DOOLEY, Kent, Conn.

INFLUENCE OF FORMALDEHYDE ON DIPHTHERIA TOXIN. I. S. SCHMIDT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:27 and 323, 1933.

The rapidity with which diphtheria toxin changes into anatoxin increases with the concentration of formaldehyde and with a rise in temperature and in the hydrogen ion concentration, and the change may become almost immediate with high concentrations of formaldehyde. Together with the change in toxicity, which is not reversible, the resistance to heat, acids, alkalis and other chemical influences increases. Because of the marked thermal instability of purified toxin, Schmidt suggests first keeping the mixture of purified toxin and formaldehyde at 0 C. and then increasing the temperature, or changing the raw toxin into anatoxin and purifying the finished product. The immunizing properties of anatoxin depend not only on its flocculating ability but on other, as yet undetermined, factors which may be due to the presence of extraneous inhibiting or stimulating substances in the medium. The technic employed in the treatment of toxin with formaldehyde may also be responsible.

DAVIDSOHN, Chicago. [ARCH. PATH.]

INFLUENCE OF VENESECTION ON THE TITER OF DIPHTHERIA ANTITOXIN. E. F. GOGIN and E. G. ZURINOWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:404, 1933.

The titer of the immune serum of horses was determined by means of the flocculation test of Glenny and Okell. The titer was highest eight days after the last injection of the antigen and dropped steadily afterward. The variations in the titer could not be correlated with any known factors. The bleeding of the horses on the eighth and tenth days proved most satisfactory; an additional third bleeding is not advisable. The amount of serum obtained at the second bleeding was from 7 to 8 per cent larger than that obtained at the first.

DAVIDSOHN, Chicago. [ARCH. Path.]

QUICK DIAGNOSIS IN EPIDEMIC CEREBROSPINAL MENINGITIS. S. I. GINSBURG, W. S. KALININ and A. P. GULJAEWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:463, 1933.

A complement-fixation test was developed by Ginsburg and his associates, employing as an antigen cerebrospinal fluid heated at 55 C. for thirty minutes. Polyvalent antimeningococcic serum served as an antibody. The performance of the test takes from three to four hours. Of 252 clinically established cases, 176 (70 per cent) were serologically, and 137 (54 per cent) bacteriologically, positive. In only 2 bacteriologically positive cases was the serologic reaction negative. In the control series of cerebrospinal fluids, including those of persons with tuberculous or pneumococcic meningitis, those with cerebrospinal syphilis and normal persons, the reaction was negative. With controls set up with the cerebrospinal fluid of patients having meningococcic meningitis, with normal horse serum and with antipneumococcic serum the results were negative, while weak positive results were obtained when antigonococcic serum was used. Precipitation tests with cerebrospinal fluid and specific antimeningococcic serum showed a much lower degree of sensitivity than the complement-fixation tests. The positive reaction became negative after termination of the disease.

DAVIDSOHN, Chicago. [ARCH. Path.]

RESEARCH AND STUDY OF DIPHTHERIA ACCORDING TO THE BLOOD GROUPING. ZOFJA LEJMBOCHOWNA, Pedjatrja polska **13**:86, 1933.

The author studied twenty families, composed of forty parents and forty-four children, in which fifty-three of the members had diphtheria and were being treated at the hospital. She came to the conclusion that a certain correlation exists between the development of diphtheria in children of parents of the same blood group and a positive Schick reaction.

KRUPINSKI, Chicago.

DEEP THERAPY IN INFANTILE MALARIA. S. YAMAMOTO, J. Pediat. (Tokyo) Dec. 20, 1933, p. 2164.

The author reports a case of tropical malaria (estivo-autumnal) in an infant, in which the condition was refractory to quinine therapy. High voltage roentgen theray was given over the splenic area. One exposure was sufficient to cause the disappearance of febrile attacks. A temperature of 40 C. (104 F.) followed the treatment, but this was only temporary. Examination of the blood since this treatment has repeatedly given negative results.

KATO, Chicago.

HAS SPECIFIC SERUM OF ADULTS ANY VALUE AS A REMEDY AGAINST WHOOPING COUGH? I. JUNDELL, Acta pædiat. **15**:1 (Nov. 6) 1933.

Undiscouraged by his previous failure to protect infants against infections of the upper respiratory tract by injections of maternal serum, Jundell in 1926 applied the same technic in both the prophylaxis and the treatment of whooping cough. His clinical material comprised twenty-three children who had been intimately exposed to pertussis. Of these, ten were given the injections during the incubation period or the early catarrhal phase of the disease. In eight the expected whooping cough failed to appear, and in two "it was only suggested." The course of the infection was influenced favorably in thirteen children treated in the beginning of the spasmodic stage. The total quantity of serum used varied between 30 and 140 cc. In each instance an elder brother or sister served as a control. Whether or not the donor had had pertussis in childhood seemed to exert no influence on the potency of the serum.

In a second series of patients, which comprises the material for the present report, the serum was obtained from adult donors who had had pertussis in childhood and who had been recently immunized by two or three intramuscular injections of whooping cough vaccine. Because of a dearth of clinical material, only five children were treated. Either an elder brother or sister or a twin living

in the same household served as a control. The treated patients were given the serum either late in the incubation period or at the onset of the catarrhal manifestations. The total quantity of serum used varied from 40 to 100 cc., and the number of injections from 2 to 5. There was an interval of from three to six days between injections. The control patients received sedatives alone.

Diagrams of the clinical course of the treated patients and the controls are presented and discussed in detail. The results, while inconclusive because of the small number of experiments, suggest that this mode of treatment may be beneficial.

The author presents concrete suggestions for conducting this type of clinical study. He asserts that closer observance of these postulates by investigators in the field will lead to more positive results than have been obtained in the past.

McCune, New York.

Chronic Infections

Tuberculosis Among Pupils of a Canadian School for Indians. Lall G. Montgomery, Am. Rev. Tuberc. **28**:502 (Oct.) 1933.

Tuberculous infection was found much more frequently in Indan than in white students. Evidences of infection may first appear as long as seven or eight years after removal from contact. The best single means of detecting tuberculous infection is the intracutaneous test, using dilutions containing 0.1 mg. of old tuberculin, the reading being taken forty-eight hours after injection. The roentgenogram is the most important factor in examination for pulmonary tuberculosis. Oblique as well as anteroposterior views should be taken. Symptoms and signs and the general appearance of the child are of little value. The finding of interlobar lines in the roentgenogram is often an indication of previous pleurisy.

Eugene Smith, Ogden, Utah.

A Further Study of Tuberculosis in Public-School Children. H. W. Hetherington, F. M. McPhedran, H. R. M. Landis and E. L. Opie, Am. Rev. Tuberc. **29**:142 (Feb.) 1934.

Additional tuberculin tests carried out in two schools in Philadelphia confirm the previous report of the high incidence of tuberculous infection. In the age group of from 15 to 19 years 79.6 per cent of white boys and 87.9 per cent of white girls and 87.9 per cent of colored boys and 86.4 per cent of colored girls reacted to tuberculin. The incidence of tuberculous lesions that threatened to undermine health was approximately 0.3 per cent in white children from 5 to 11 years of age and more than five times as great in colored children of the same age. The incidence of serious tuberculous lesions in children from 12 to 20 years of age was 1 per cent for white boys and 2.3 per cent for white girls.

Eugene Smith, Ogden, Utah.

Corrected Sedimentation Rate (C.S.R.) in Pulmonary Tuberculosis. Samuel Friedman, Am. Rev. Tuberc. **29**:198 (Feb.) 1934.

Friedman is convinced that the sedimentation test reported by means of the C.S.R. should become the most important aid in the management of pulmonary tuberculosis. It is a reliable index of activity and serves as an index when other phenomena, such as the temperature and weight curve, cease to be of value. It is certainly of greater value in determining the actual increase or decrease of pathologic activity than are the x-rays. It gives information not as to the spread of the disease anatomically, but in quantitative terms. In convalescence the C.S.R. is the most important single piece of information as to the progress of the patient. It should also be a valuable aid in the diagnosis in early and doubtful cases.

Eugene Smith, Ogden, Utah.

THE LINZENMEIER BLOOD SEDIMENTATION TIME IN TUBERCULOUS CHILDREN. WILLIAM ANTHONY REILLY, Am. Rev. Tuberc. **29**:220 (Feb.) 1934.

The Linzenmeier red cell sedimentation test done on thirty-six tuberculous girls one hundred and four times was found to be a more reliable procedure in the prognosis than in the diagnosis of tuberculous activity. It is also of presumptive aid in diagnosing activity. The author believes that it has an advantage over the usual signs, symptoms and laboratory procedures in determining activity.

EUGENE SMITH, Ogden, Utah.

THE EARLY DIAGNOSIS OF POTT'S DISEASE. R. I. HARRIS, Am. Rev. Tuberc. **29**: 223 (Feb.) 1934.

Pott's disease, being hematogenous in origin, appears only in patients who have tuberculosis elsewhere than in the spine. It is a potential possibility in every patient under treatment for tuberculosis. The symptom most valuable for early diagnosis is spinal pain, which is increased by activity and weight-bearing and relieved by rest, experienced not only in the diseased area but referred also to spinal segments corresponding in level to the diseased vertebrae. Other symptoms are: muscular spasm, deformity, abscess formation, characteristic roentgenographic appearance and paraplegia.

EUGENE SMITH, Ogden, Utah.

PATHOLOGICAL FINDINGS AND PATHOGENESIS OF CONGENITAL TUBERCULOSIS. MORRIS SIEGEL, Am. Rev. Tuberc. **29**:297 (March) 1934.

Congenital tuberculosis may be defined as tuberculosis in which the infection occurs before birth by way of the blood stream or at birth by the aspiration of tuberculous amniotic fluid or tuberculous matter present in the birth canal. Thirty-eight cases of undoubted or probable congenital tuberculosis reported in literature were studied by the author. The tuberculous organs were usually the lungs, liver and spleen and, after a certain age, the intestines. Microscopically, the lesions were reported as tubercles, except in the lungs, where tuberculous pneumonic areas were not uncommon. Caseation was common; cavitation, ulceration and calcification were also mentioned. In the few cases in which primary lesions were specifically reported they were described as localized caseous areas in the lungs or liver. The lungs were most frequently involved. Occasonally the lesions in the liver were more marked than those in the lungs. Involvement of the liver and spleen went side by side. The degree of hepatic involvement was most marked in patients who died within the first two weeks of life. Lesions in the gastro-intestinal tract were seen in 70 per cent of the patients 39 days of age or older, all of whom had advanced pulmonary tuberculosis. The lymph nodes usually involved were the pulmonary, mesenteric and portal, in the order of frequency. Acute tuberculous leptomeningitis was reported in one case.

EUGENE SMITH, Ogden, Utah.

TUBERCULIN TESTS IN CHILDREN. HENRY A. REISMAN, New York State J. Med. **33**:734 (June 15) 1933.

The subject of cutaneous tests for tuberculosis is discussed. It is especially necessary to know whether the tuberculin used is reliable and potent. The human tubercle bacillus protein known as M A 100 gives the same cutaneous reactions as Koch's O T and is more easily standardized.

AIKMAN, Rochester, N. Y.

EPITUBERCULOSIS. H. A. V. LOOTS, South African M. J. **7**:214 (April 8) 1933.

Epituberculosis is a benign tuberculous infiltration of the lung. It was first described by Eliasburg and Neuland. This type of tuberculosis is given as the eighth type of tuberculous disease in children, the others being: the bronchial and hilar gland type, tuberculous bronchopneumonia, miliary tuberculosis, meningeal

tuberculosis, abdominal tuberculosis, pleural tuberculosis and lesions of the bones and joints. By epituberculosis is meant a nonspecific inflammatory reaction around a tuberculous focus, such as a primary focus of Ghon. It gives rise to consolidation of the pulmonary tissue, the consolidation being allergic in nature. Roentgenograms show uniform consolidation without signs of infection in other pulmonary areas. There are well marked dulness to percussion and bronchial breathing. The disease occurs during the first three years of life and lasts from several months to one year; the patient always recovers. There are little or no fever and no bacilli in the sputum or stool. Proof of tuberculous origin is given as (1) a positive Mantoux reaction, (2) a history of frequent contact and (3) the demonstration of tubercle bacilli in material aspirated from the consolidated area.

GONCE, Madison, Wis.

THE VERNES SERO-FLOCCULATION TEST FOR TUBERCULOSIS. R. MURRAY, South African M. J. **7**:645 (Oct. 14) 1933.

Murray found that: (1) the Vernes test is not specific for tuberculosis, (2) the sedimentation rate and the Vernes test are not related in any simple way and (3) in cases in which recovery from tuberculosis is taking place the sedimentation test gives a normal reading sooner than the Vernes test.

GONCE, Madison, Wis.

BRONCHIAL DILATATION AND STIGMA OF HEREDITARY SYPHILIS WITH A NEGATIVE TUBERCULIN REACTION. M. ARMAND-DELILLE and GAVOIS, Bull. Soc. de pédiat. de Paris **31**:137 (March 21) 1933.

A boy, 8½ years old, had a marked cough and expectorated greenish-yellow purulent sputum. The fingers were clubbed and the nails markedly curved. Sibilant and subcrepitant râles were present in the base of both lungs. Roentgenologic examination after the injection of iodized poppy-seed oil 40 per cent showed the presence of bronchiectasis at the base of the left lung. Because of certain stigmas, even though the Wassermann reaction of the blood was negative, the patient was considered to have congenital syphilis, which is believed to be a predisposing factor in cases of bronchiectasis. A third case of this kind which was observed by the authors revealed evidence of syphilis. This child had measles at the age of 8 months, which was followed soon after by whooping cough; the possibility that these diseases played some part in the development of bronchiectasis is mentioned. Examination of the sputum showed no tubercle bacilli, and the tuberculin reaction was negative.

BENJAMIN, Montreal, Canada.

PRESENCE OF TUBERCULOUS VIRUS IN THE CIRCULATING BLOOD OF A CHILD HAVING RHEUMATIC ENDOCARDITIS. J. VALTIS, G. PAISSEAU and F. VAN DEIUSE, Compt. rend. Soc. de biol. **112**:742 (March 3) 1933.

A 7 year old child on examination showed a definite mitral murmur with signs of insufficiency. A culture of the blood was made, and acid-fast bacilli were grown according to the method of Löwenstein. Subsequently these organisms, after having been injected into guinea-pigs which showed negative tuberculin reactions, produced typical pathologic tuberculosis. There is no mention made of the relation of this blood finding to the endocarditis.

WAHL, Cleveland.

SCROFULA. A. B. MARFAN, Nourrisson **21**:337 (Nov.) 1933.

Marfan believes that scrofula continues to be a valuable term in the nosology of tuberculosis and should not be discarded. It indicates a special type of tuberculosis in children who seem to possess partial immunity; the disease runs a benign course and eventually confers a high degree of immunity so that those recovering seem to be free from the danger of subsequently contracting the serious forms of pulmonary tuberculosis. The similarity between scrofula and the reactions

encountered after vaccination with B C G is described. Mention is made of the high degree of sensitiveness to tuberculin in scrofulous persons; the tuberculous nature of phlyctenular conjunctivitis is also discussed.

McCLELLAND, Cleveland.

SYPHILITIC PERIOSTITIS. G. BLECHMANN and P. J. MENARD, Nourrisson **22**:168 (May) 1934.

Periostitis of the tibia appeared in an infant aged 2 months who otherwise was normal but had gained only slowly in weight. The diagnosis of periostitis was confirmed by a roentgenogram.

Mercury rubs produced a functional cure within forty days.

McCLELLAND, Cleveland.

SYPHILITIC CONTAMINATION OF THE EMBRYO AND THE FETUS: ACTUAL STATE OF THE QUESTION. M. PÉHU and G. PIZZERA, Rev. franç. de pédiat. **9**:401, 1933.

This article is divided into two parts, the first discussing the known facts regarding this type of syphilitic infection and the second discussing questions which are as yet unsettled.

It is established that in the great majority of cases syphilis in the mother is responsible for syphilis in the offspring. Whatever the duration of her syphilis and whatever the character of her infection, whether it is latent or virulent, a syphilitic mother is always likely to contaminate her infant. The infection takes place through the blood stream, passing the placental barrier. Occasionally this may occur at the time of labor. An infant may also acquire syphilis at the time of labor in the form of a primary chancre. The child of a syphilitic mother is almost always syphilitic: there are, however, occasional exceptions. This does not invalidate the statement of Profeta that a child of syphilitic parents should be nursed by his mother, even though he appears clinically normal. Conversely, the mother of a syphilitic child is almost always herself syphilitic. Exceptions to this have been reported by reliable investigators, and in such instances the mother should express the milk from her breasts and give it to the child from a bottle.

The last observation leads to the question of whether syphilis can be transmitted by the sperm, the mother remaining uninfected. Clinical observations in support of this have been reported from time to time, but were discredited because one could not conceive of the spirochete being contained in the head of the spermatozoon. Recent observations point to the possibility that the spirochete of syphilis may exist in a granular or in an invisible form. Since the spirochete itself is never found in the embryo before the fourth or fifth month, the existence of such a form would be essential to the proof of paternal transmission. This question is still open.

LESLIE, Evanston, Ill.

DISTRIBUTION OF CONGENITAL SYPHILIS IN ITALY. BRUNO PINCHERLE, Pediatria **42**:48 (Jan. 1) 1934.

The author demonstrates the difficulty of deducting from official statistical data any accurate conclusion concerning the distribution of congenital syphilis in Italy. The percentage of infants with congenital syphilis found among those brought for admission to hospitals, as well as among those frequenting the outpatient services in nine Italian cities, is reported. These data suggest strongly that the disease is more frequent than has heretofore been believed and that prophylaxis must be notably intensified in this field.

SIGNORELLI, New Orleans.

TWO UNUSUAL CASES OF CONGENITAL SYPHILIS. D. MOGGI, Riv. di clin. pediat. **31**:1443 (Dec.) 1933.

Moggi reports two cases of congenital syphilis in babies. In one, an infant of 40 days, convulsions had begun at the age of 11 days; the spinal fluid was of the consistency of ground glass and contained many lymphocytes. The child

responded well to treatment with mercurial inunctions and neoarsphenamine. The other baby was 38 days old and had not moved the right arm. A roentgenogram showed not only periostitis but also considerable osteomyelitis. This proved to be a syphilitic condition and responded to treatment. HIGGINS, Boston.

PULMONARY TUBERCULOSIS OF BENIGN CHARACTER CAUSED BY B C G. ALVIMAR DE CARVALHO, Pediatria, Rio de Janeiro **1**:10 (Jan.) 1934.

An infant of the exudative diathesis type was vaccinated by mouth at 10 days of age. During the next two years a pulmonary reaction developed that is clearly shown by a roentgenogram. This caused no effect on the general well-being. The author believes this to have been due to the B C G vaccine, because of the absence of elevation of temperature and symptoms, inability to find the bacilli in any secretions and, finally, the complete disappearance of the lesions. He believes that the vaccine was possibly too strong, and that this, coupled with an abnormal constitutional condition (exudative diathesis), brought about the reaction.

SANFORD, Chicago.

DETERMINATION OF TUBERCLE BACILLEMIA IN CHILDREN. JOSEPH SIEGL, Beitr. z. Klin. d. Tuberk. **81**:557, 1932.

Siegl sent equal parts of identical blood specimens to Dr. Löwenstein and Dr. Maresch for cultivation of tubercle bacilli by Löwensten's method. A third aliquot portion was sedimented and injected into guinea-pigs. The specimens were obtained from one hundred and forty children; some of these had active tuberculosis; others reacted positively to tuberculin but had clinically inactive tuberculosis, and the remainder showed negative reaction to tuberculin. Dr. Löwenstein's laboratory reported 13.5 per cent positive cultures for those with active tuberculosis, 18.9 per cent positive results for those with inactive tuberculosis and 23.9 per cent positive findings for those with negative tuberculin tests. Dr. Maresch's laboratory reported that 5.1 per cent of the specimens contained tubercle bacilli, and these specimens were all from children with active tuberculosis. Moreover, only once did both these experimenters isolate tubercle bacilli from the same person's blood. Also, only one guinea-pig presented tuberculosis following inoculation and that from a specimen which both laboratories had reported as negative. Siegl also distributed urine, sputum and pus containing tubercle bacilli to the same two laboratories, and although many positive results were reported, in only three specimens did both laboratories report identical results. Of the eleven positive cultures that Löwenstein reported for children who showed a negative reaction to tuberculin, six produced typical tuberculosis in guinea-pigs. Siegl concludes that it is not as yet possible to resolve these contradictions.

MARGULIS, Tucson, Ariz. [ARCH. PATH.]

BRONCHIOGENIC TUBERCULOSIS IN CHILDREN. L. DE VELASCO, Beitr. z. Klin. d. Tuberk. **81**:675, 1932.

The author investigated the significance of bronchiogenic propagation in the development of pulmonary tuberculosis in childhood. The material consisted of thirty-two children, aged from 9 months to 6 years, who came to autopsy. Thirteen showed undoubted evidence of extension by the bronchiogenic route. In general, these bronchiogenic foci showed the same differentiation into those due to small seedings and those due to coarse seedings as Loeschcke has described in adults. In eight cases the source of the propagation was excavation of a primary focus, while in six cases a caseated lymph node had ruptured into a bronchus. In the absence of evidences of hematogenous dissemination, however, caseation of lymph nodes was slight, and intranodular hemorrhagic foci were absent. This likewise parallels the histologic picture of the disease in adults.

MARGULIS, Tucson, Ariz. [ARCH. PATH.]

TUBERCLE BACILLI IN THE BLOOD AND CEREBROSPINAL FLUID IN CHOREA. E. LOEWENSTEIN, Wien. klin. Wchnschr. **46**:1286 (Oct. 27) 1933.

Loewenstein reports that in two cases of chorea the tubercle bacilli were grown from the cerebrospinal fluid in pure culture. In one case, that of a patient who had been suffering from chorea for more than a year, the blood culture was negative, and only the spinal fluid gave a positive culture. In the other case tubercle bacilli were cultured from both the blood and the spinal fluid.

Loewenstein mentions two other cases in which positive cultures of tubercle bacilli were obtained from the spinal fluid of children suffering from chorea, the blood giving a positive culture in one of these cases also. ABT, Chicago.

TREATMENT OF CONGENITAL SYPHILIS. S. SAWADA, J. Pediat. (Tokyo), Nov. 20, 1933, no. 402, p. 2034.

Sawada reports favorable results of the oral administration of 4-oxyacetylaminophenylarsenic acid, containing 27.3 per cent of arsenic. He saw the Wassermann reaction of fourteen of eighteen patients with congenital syphilis become negative with this treatment. KATO, Chicago.

Internal Diseases

THE RENAL LESIONS OF RHEUMATIC FEVER. J. L. BLAISDELL, Am. J. Path. **10**:287 (March) 1934.

In eight of sixteen proved cases of rheumatic fever the author found acute nonsuppurative inflammation of the adventitial tissues of the smaller arteries and arterioles of the kidney. Involvement of the media was rare. Glomerular changes are to be regarded as secondary to vascular changes. MOORE, New York.

POLYARTERITIS NODOSA. R. B. HAINING and T. S. KIMBALL, Am. J. Path. **10**:349 (May) 1934.

The term "polyarteritis nodosa" is proposed as more descriptive than "periarteritis nodosa." Any organ or combination of organs may be affected. The visceral arteries are affected more commonly than those of the extremities. The organs most commonly affected are the kidneys, heart, gastro-intestinal tract, pancreas, muscles, peripheral nerves, liver, spleen and cerebrum. All the coats of the blood vessels are involved, and destruction of the media may lead to an aneurysm. Involvement of the intima may induce thrombosis. The disease is progressive and chronic, and acute lesions may be found. A specific filtrable virus with affinity for the small and medium-sized arteries is probably the cause. Cases have been reported with remission of the symptoms following the intravenous administration of arsenicals. One case in a 49 year old Negro is reported in detail. MOORE, New York.

CARDIAC COMPLICATIONS OF TRICHTERBRUST. JAMES G. CARR, Ann. Int. Med. **6**:885 (Jan.) 1933.

Funnel breast results in progressive enlargement of the transverse diameter of the chest as the depression is deepened. This, in turn, results in displacement of various organs and interferes with their function. This article deals mainly with the anatomic and physiologic effects on the heart produced by this condition. Dyspnea and palpitation are the most common cardiac symptoms. Although definite cardiac symptoms are not the rule in these cases, they are not infrequent. Cases have recently been reported in which operative procedures were followed by relief of the symptoms. READING, Galveston, Texas.

BILATERAL SPLANCHNIC NERVE SECTION IN A JUVENILE DIABETIC. GÉZA DE TAKÁTS and G. K. FENN, Ann. Int. Med. **7**:422 (Oct.) 1933.

The case of an 18 year old colored girl is reported, on whom a bilateral section of the splanchnic nerve was performed because of severe diabetes mellitus. The reasons for doing this instead of denervation of the adrenal gland are given. This patient was selected because she had a severe type of juvenile diabetes and an unstable dextrose tolerance and because the condition had existed for at least two years. The operation resulted in an abrupt change of the dextrose-insulin ratio from 2.5:1 to 5:1. This change occurred after section of the left splanchnic nerve. Later, section of the right splanchnic nerve resulted in no further improvement. Following the operation the patient gained weight.

READING, Galveston, Texas.

RATIONAL TREATMENT OF THE ANEMIC PATIENT. WILLIAM B. MURPHY, Ann. Int. Med. **7**:939 (Feb.) 1934.

The author states that the best treatment is that which is adequate and which is available at a minimum of inconvenience and expense. He discusses both pernicious and secondary (hypochromic) anemia. In the latter condition, which is a result of iron deficiency, studies carried on over a period of several years indicate that ferrous carbonate (1.8 Gm. daily) or ferric ammonium citrate (3.0 Gm. daily) in large doses are more effective than ferric citrate. The author calls attention to the fact that when whole liver is given in addition to the iron the effect is better than when either is given alone. Liver extracts, when taken perorally, are not effective, as compared with the results of whole liver therapy, but when given intramuscularly, in combination with large doses of iron taken perorally, the response in the production of hemoglobin and red blood cells is more rapid than when similar amounts of iron are used alone. The author found that the preparations containing iron and copper showed no effects greater than those which might be expected from the iron contained therein.

As a result of this study, the conclusions reached were that combinations of liver extract, ventriculin, copper, vitamins, etc., given together with iron, are not necessary, as it has not yet been proved that such combinations are more effective in anemia in man than the iron contained therein, and that such combinations are much less palatable and many times more expensive than iron in simple form.

READING, Galveston, Texas.

LIPOID PNEUMONIA. JACOB RABINOVITCH and MAX LEDERER, Arch. Path. **17**:160 (Feb.) 1934.

Six cases of lipoid pneumonia are reported, with complete observations post mortem. The anatomic changes produced in the lungs by oil consist chiefly of large monocytic cell infiltration, granulomatous formation and, finally, connective tissue proliferation. The authors warn against the use of oily substances administered to children by way of the nasopharynx. The greater part of the oil is engulfed by monocytes and either expectorated or carried to the regional lymphatics, although some of the oil may be encysted in granulomatous tissue. It is suggested that the diagnosis of lipoid pneumonia can be made in a certain number of cases by the examination of expectorated material for oil in the monocytic cells.

LEMASTER, Evanston, Ill.

DIABETES MELLITUS—PROBLEMS OF PRESENT DAY TREATMENT. HERMAN O. MOSENTHAL, Bull. New York Acad. Med. **9**:505 (Sept.) 1933.

This article is a discussion of the latest developments in diabetes, with records and charts showing statistical factors in the disease, the changing tendencies in the age groupings and the principles of the treatment. The article is followed by a discussion of public health phases by Dr. Charles Bolduan, who

cites valuable incidents in the development of diagnostic criteria of the disease touching on the relatively increased frequency. A point is raised in regard to the health department's efforts to help in the control of this condition.

Heredity and prevention are discussed by Dr. Elliott P. Joslin, who urges that diabetes is a disease which must be controlled by physicians and not by the state or city. He advises the physician to focus on the family for the prevention of diabetes, because heredity is the most important factor in its etiology, and to focus on the patient to prevent complications.

The clinical phases are discussed by Dr. Nellis B. Foster. The author pleads for sane thinking in connection with diet and insulin. There is no such thing as a standard diet for a diabetic patient, since two persons of approximately the same weight, height and age may differ by as much as 50 per cent in regard to the rations required to keep in a state of good nutrition. Each patient, therefore, is a problem, and the treatment must be based on the patient's well-being and not on dogmatic teachings. Nor should the psychic state of the diabetic patient be neglected. It is necessary to educate the patient to live in harmony with his disease, and in the child the formalities are comparatively easily cultivated into habits which sink into the background of consciousness.

Recent trends in the mortality in diabetes are illustrated by Dr. Dublin.

JAHR, Omaha.

THE CLINICAL APPLICATION OF HAEMATOLOGY TO INFANTS AND CHILDREN. CHARLES E. SNELLING and MAX ALAN BROWN, Canad. M. A. J. **30**:488 (May) 1934.

This article is an excellent résumé of hematologic data regarding various pathologic states in the normal infant and child.

MOORE, Omaha.

THE CLINICAL USE OF PROLACTIN. R. KURZROK, R. W. BATES, O. RIDDLE and E. G. MILLER, Endocrinology **18**:18 (Jan.-Feb.) 1934.

Thirty-seven women delivered of normal children at the Sloane Hospital for Women in New York City were treated with intramuscular injections of an anterior pituitary hormone in two doses varying from 2.5 to 10 cc. (from 75 to 400 units) given from twelve to twenty-four hours apart.

In eight of the cases no conclusions could be drawn, but in twenty-nine in which lactation had failed to develop adequately by the sixth day or later post partum it was considered that a definite increase in the amount of milk following injections might be definitely attributed to this medication. In twenty-one of these cases there was a gain greater than 100 Gm. of breast milk daily, in four a gain of from 50 to 100 Gm. and in 4 no increase. Injections of the hormone produced no local or general reactions and no postpartum complications.

On the basis of these results, the clinical dose of the hormone is provisionally considered an initial dose of 150 units, followed within from twelve to twenty-four hours by 100 units.

JACOBSEN, Buffalo.

DISEASES, MALFORMATIONS AND INJURIES OF THE MOUTH AND ASSOCIATED PARTS OCCURRING IN CHILDREN. MALCOLM WALLACE CARR, Internat. Clin. **4**:233 (Dec.) 1933.

Oral pathologic conditions, in an attempt to correlate the principles of oral surgery with the practice of pediatrics, may be divided as follows:

1. Primary infection and inflammation of the soft tissues of the mouth
   (a) Inflammatory reaction of deciduous dentition in the majority of healthy children produces little or no disturbance. Lancing of the gums is contraindicated.
   (b) Peridontal disease, often associated with the deposition of subgingival salivary calculus. This may constitute a focus of infection.

(c) Aphthous stomatitis is treated with silver nitrate, 10 per cent.
(d) Ulcerative stomatitis—the result of poor hygiene.
(e) In gangrenous stomatitis, the destruction of tissues extends deeper than the mucous membrane. There may be massive destruction of various structures of the mouth, with diffuse cervical adenitis. The mortality is 50 per cent.
(f) Noma (cancrum oris) is a progressive gangrene which occurs between 3 and 12 years. It is probably due to vascular thrombosis caused by invasion of Vincent's organism and is usually fatal.
(g) Vincent's stomatitis may be complicated by fusospirochetal infections of the eye, ear, mastoid, sinuses and lungs.
(h) The certain diagnosis of thrush is made microscopically. Boric acid therapy is effective.

2. Oral manifestations of systemic disease
(a) Local lesions manifest before systemic disease in the acute exanthems, leukemia and agranulocytic angina.
(d) The ingestion of drugs, such as mercury, bismuth and arsphenamine, produces stomatitis.
(c) Oral lesions in specific diseases, such as syphilis, tuberculosis and actinomycosis.
(d) Oral lesions in diseases of dietary deficiency, which are typified by rachitic teeth.

3. Infections of the teeth, periapical regions and adjacent tissues
(a) Dental caries consists of the chemical solution of calcium salts by lactic acid, followed by decomposition of the organic matrix. Diet and nutrition are important factors. Prophylactic care and treatment of deciduous teeth are necessary to prevent serious infection and malocclusion.
(b) Chronic periapical disease produced by the passage of infection through the apex. This is usually due to Streptococcus.
(c) Acute dento-alveolar abscess may burrow in different directions and may perforate into the mouth or nose or terminate in acute cellulitis or osteomyelitis.

4. Abnormalities of growth and development
(a) Malocclusion. Moderate irregularity of teeth anterior to the first permanent molar is usually corrected spontaneously. Untreated malrelations between maxillary and mandibular first molars are followed by malrelation of jaws. Adenoids are an important factor. Early orthodontic treatment is imperative.
(b) Supernumerary teeth should usually be removed.
(c) Impacted teeth should usually be treated conservatively. Room for eruption may be provided by orthodontic appliances. If the teeth are only partially erupted, they should usually be extracted.
(d) Harelip and cleft palate.

5. Benign and malignant tumors
(a) Hypertrophy of the gums—possibly a deficiency disease.
(b) Epilus, a benign, giant cell sarcoma, does not metastasize. It is cured by removal.
(c) Sarcoma is the most frequent malignant growth arising from the mouth or maxillary bones.
(d) Benign odontoma of several types arises from embryonic cells.

6. Traumatic injury
(a) Fracture is the most common injury. It is treated by reduction and immobilization.

MILLER, South Bend, Ind.

A Study of the Occurrence of Unfertilized Ascaris Eggs. A. E. Keller, J. Lab. & Clin. Med. **18**:371 (Jan.) 1933.

In a study of 1,103 fecal specimens containing ova of Ascaris lumbricoides, Keller found unfertilized ova in 26.2 per cent, fertilized ova in 32.2 per cent and both fertilized and unfertilized ova in 41.6 per cent. The importance of the large number of stools in which unfertilized ova were found lies in the fact that such ova are frequently missed in the examination of stools, and thus the diagnosis is overlooked.

McMurray, Galveston, Texas.

Results of Treatment in Rheumatoid Arthritis with Reference to Foci of Infection and Streptococcus Vaccine. W. J. Stainsby and E. E. Nicholls, J. Lab. & Clin. Med. **18**:881 (June) 1933.

A study was attempted to evaluate the efficacy of removal of foci of infections and the use of streptococcic vaccine in the treatment of rheumatoid arthritis. Because of the small number of cases which showed other foci of infection, this study includes only cases in which tonsillectomy was performed. In the groups in which tonsillectomy alone was performed—103 patients—58.3 per cent showed improvement. In the group of 194 patients who received only vaccine therapy 35.6 per cent showed improvement. In patients who received both forms of treatment the percentage showing improvement was no higher than for those on whom only tonsillectomy was performed. As was to be expected, the younger the patient and the milder the symptoms the better the results were. The duration of the disease did not appear to enter into the possibility of recovery.

McMurray, Galveston, Texas.

Comparative Value of the Intradermal and Ophthalmic Tests of Sensitiveness to Horse Serum. L. Taft, J. Lab. & Clin. Med. **18**:1160 (July) 1933.

In a series of 126 patients who had never received any injections of horse serum a cutaneous reaction to horse serum was positive in 4 per cent and an ophthalmic reaction in 0.8 per cent. In a group of 229 who had at some time received injections of horse serum there was a positive cutaneous reaction in 44.7 per cent, whereas the ophthalmic reaction was positive in only 15 per cent. A discussion of the technic of these tests is given. The author concludes that the skin test is much more reliable and that it is the test of choice for sensitivity to horse serum.

McMurray, Galveston, Texas.

The Relative Incidence of Intestinal Parasites in Hospital Patients in Nashville and in Rural Tennessee. H. E. Meleney, J. Lab. & Clin. Med. **19**:113 (Nov.) 1933.

Examinations of feces for animal parasites were made as a routine in a series of 2,112 hospital patients. It was found that urban patients showed fewer parasites than did patients from immediately around the city, and that, in turn, strictly rural patients showed a still higher incidence of parasites. This difference is explained on the basis of the more sanitary disposal of excreta in cities, fewer flies and better personal hygiene. The statistics were compared with reports from hospitals in other cities, and it was found that, as a general rule, the percentage of intestinal parasites increases as one goes from Northern to Southern cities.

McMurray, Galveston, Texas.

Further Studies on the Cultivation of Endameba Histolytica and a Complement Fixation Test for Amebiasis. H. Tsuchiya, J. Lab. & Clin. Med. **19**:495 (Feb.) 1934.

A new culture medium composed of nutrient broth and a mixture of starch and charcoal with or without Dorsett's egg medium is described. There are

two distinct advantages of this medium: first, it is simpler than other mediums and, second, amebas other than Endamoeba histolytica will not grow on it.

An antigen was prepared from amebas grown on this medium, and complement-fixation tests were carried out with this antigen. In a control group of one hundred and fifty-three persons known to be free from amebae all the subjects gave negative reactions. A second group of eighteen persons was examined. Eight of these were known carriers of E. histolytica, and all these gave positive reactions. One patient gave negative reactions repeatedly. Four patients with ulcerative colitis, for whom examination of the stools gave repeatedly negative results, showed positive reactions.

A negative reaction is an important factor in ruling out amebiasis, while a positive reaction is a valuable factor in its diagnosis.

McMURRAY, Galveston, Texas.

SICKLE CELL ANEMIA. R. H. McCLELLAN and R. M. ENTWISLE, J. Lab. & Clin. Med. **19**:507 (Feb.) 1934.

The authors report a case of sickle cell anemia in a 10 year old Negro boy. This child had always been "delicate"; his chief disorder was a chronic ulcer of the leg. In addition to this ulcer, examination showed jaundice of the scleras, enlargement of the heart, systolic mitral murmur with a thrill, enlargement of the liver, no splenic enlargement and anemia. The red cells showed sickling in both wet and stained preparations. Transfusions gave only temporary relief. Splenectomy was performed. The child died on the third day of postoperative pneumonia. Permission for an autopsy was not obtained. McMURRAY, Galveston, Texas.

INTRACRANIAL HEMORRHAGE IN PURPURA HEMORRHAGICA. B. J. ALPERS and WILLIAM DUANE, J. Nerv. & Ment. Dis. **78**:260 (Sept.) 1933.

Two cases of purpura haemorrhagica are reported, one in a man, aged 47, the other in a girl, aged 4 years. The latter patient had a long history of purpuric spots in the skin and mucous membranes; intestinal hemorrhage, with the development of headache, and blurred vision, but with no localizing cerebral signs. The length of her first stay in the hospital was thirteen days, during which time she was given roentgen and ultraviolet ray treatment. The diagnosis on dismissal was chronic purpura. The patient was readmitted eight days later because of hemorrhages from the bowels. She remained in the hospital sixty days and was discharged slightly improved. She was readmitted twenty-four days later because of severe frontal and occipital headache and blurring of vision. The spinal fluid pressure was 70 mm. of mercury; the fluid was yellow and contained 648 red cells per cubic millimeter. The same day the pressure declined to 20 mm., and the red cell count rose to 2,592. The platelet count was 2,800. Seven days later the platelet count was 13,000. Splenectomy was performed, with little improvement. The spinal fluid pressure remained high; the temperature was 107 F. The respiration rate became rapid, and the patient died.

The diagnosis of hemorrhage with purpura is not difficult to make, if one elicits a careful history of general bleeding combined with symptoms of intracranial pressure. Lumbar puncture verifies the diagnosis. The prognosis is unfavorable.

JAHR, Omaha.

THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN WITH ANTI-PNEUMOCOCCUS SERUM. ROSA LEE NEMIR, J. Pediat. **3**:827 (Dec.) 1933.

Of two hundred and seven children with lobar pneumonia or bronchopneumonia, eighty-two were given antipneumococcic serum. The pneumococci were typed from cultures from laryngeal swabs, and only specific serum for the one type was used in each case. The serum was given intravenously and, in some cases, intramuscularly, in repeated, small doses. The mortality rate of the combined group of those with lobar pneumonia and those with bronchopneumonia was 9.8

for those receiving serum, as compared to 16.6 in the untreated cases. Most striking was the effect of the serum in hastening the onset of the crisis in lobar pneumonia.

The best results were obtained in pneumonia due to Pneumococcus types I and XIV. The clinical impression was that the toxicity decreased rapidly after the patient received the serum intravenously. Delayed serum reactions occurred frequently.

LeMaster, Evanston, Ill.

Chronic Interstitial Nephritis with Dwarfism. J. W. Amesse and Mervin H. Black, J. Pediat. **3**:902 (Dec.) 1933.

A case of renal dwarfism in a 4 year old Jewish girl is reported. The child was extremely small but symmetrically developed. Her body weight was 14½ pounds (6.6 Kg.), and her height was 28½ inches (72.4 cm.). The circumference of the head was 15½ inches (39.4 cm.), that of the abdomen 15 inches (38.1 cm.) and that of the chest 16½ inches (41.9 cm.). Urinalysis repeatedly showed albumin (four plus) and hyaline casts. The bones were normally calcified, and the epiphyses were normally ossified for the age. The child's mother was a morphine addict.

LeMaster, Evanston, Ill.

Disorders of Internal Gland Secretion in Children. Fritz B. Talbot, J. Pediat. **3**:909 (Dec.) 1933.

The most important contributions to the field of endocrinology during the past year are briefly discussed in this critical review. It is suggested that all reports of basal metabolism be recorded in terms of total production of heat so that data from various sources may be accurately interpreted by known standards. Evidence of the interrelation of the endocrine glands has become greater than ever. Each of the internal glands is briefly considered, with especial emphasis on the pituitary gland.

LeMaster, Evanston, Ill.

A Study of Nephrosis in Children. F. Harold Westcott and Roger H. Dennett, J. Pediat. **4**:191 (Feb.) 1934.

Five selected cases of nephrosis in children are discussed clinically. The pathology is essentially that of lipoidal degeneration with a superimposed infectious element. The disease is considered as a metabolic disorder of unknown etiology. The scheme of treatment employed by the authors is presented.

LeMaster, Evanston, Ill.

The Serum Treatment of Pneumonia in Children. Camille Kereszturi and David Hauptmann, J. Pediat. **4**:331 (March) 1934.

One hundred and thirty-one infants and children with pneumonia were studied over a period of two years. Pneumococcus types XIV and I were most frequently found in lobar pneumonia, whereas type XIX was most common in bronchopneumonia. Two thirds of the patients had lobar pneumonia, with a mortality of 20 per cent. Six per cent of the patients yielded positive blood cultures. Statistically, there was no evidence that the serum treatment reduced the death rate.

LeMaster, Evanston, Ill.

Renal Rickets. George B. Bader, J. Pediat. **4**:368 (March) 1934.

Two cases of renal rickets in brothers, aged 9½ and 6 years, respectively, are reported. The observations at autopsy on the older brother are included. A short general discussion of renal rickets is offered.

LeMaster, Evanston, Ill.

LYMPHANGIECTASIS WITH CHYLORRHEA. HENRY G. PONCHER and THOMAS P. SALTIEL, J. Pediat. **4**:387 (March) 1934.

A case of lymphangiectasis with chylorrhea in a colored boy, 11 years old, is reported. The upper part of the left thigh was swollen, and an intermittent milky-white discharge exuded from small vesicles in the left groin. The tuberculin reaction was negative, but the Wassermann and Kahn reactions of the blood were four plus.

Exploratory laparotomy revealed enlarged mesenteric lymph glands, which histologically showed changes characteristic of chronic lymphadenitis. One explanation of the cause of this condition is that an enlarged syphilitic gland may obstruct the flow of chyle into the thoracic duct and thus produce a retrograde flow into the iliac and inguinal vessels, which are superficial and easily ruptured by the back pressure.

LEMASTER, Evanston, Ill.

ALLERGIC DISEASES. FRANCIS SCOTT SMYTH, J. Pediat. **4**:410 (March) 1934.

The contributions to the literature on allergic diseases during 1933 are briefly cited and discussed in this critical review. The subject matter is grouped under the following headings: general considerations and constitutional studies, diagnosis and technic, bacterial allergy and dermatoses. The bibliography includes eighty-one references.

LEMASTER, Evanston, Ill.

NEUROCYTOMA OF THE ADRENAL GLAND WITH METASTASIS. HENRY S. MEYER, J. Pediat. **4**:517 (April) 1934.

The author reports the case of a 3 year old boy with a neurocytoma of the right suprarenal gland, showing metastasis in all the long bones with complete observations at autopsy. Reproductions of x-ray films are included.

LEMASTER, Evanston, Ill.

BENIGN OR FUNCTIONAL ALBUMINURIA IN CHILDREN. JOSEPH K. CALVIN, J. Pediat. **4**:611 (May) 1934.

In most cases of albuminuria in otherwise healthy children the condition is harmless, benign and relatively transient and should not be stressed to either the patient or the parent. However, organic changes must be ruled out by the physician in every case. No specific treatment is required, but malformation, defective posture and foci of infection should be treated as usual.

In boys with and without albuminuria, prostatic and vesicular massage failed to produce any appreciable amount of protein in the urine.

LEMASTER, Evanston, Ill.

THE USE OF COPPER AND IRON IN THE TREATMENT OF SECONDARY ANEMIA IN CHILDREN. JOHN F. CASON, J. Pediat. **4**:614 (May) 1934.

In a small series of children with secondary anemia a cupric and ferric compound was found to give as good results as a cuprous and ferrous compound. A ratio of copper to iron of 1:25 did not cause gastric disturbance.

LEMASTER, Evanston, Ill.

DIABETES MELLITUS IN CHILDREN. ALVAH L. NEWCOMB, J. Pediat. **4**:617 (May) 1934.

Sixty-five cases of diabetes mellitus in children observed by the author were studied. The highest incidence of onset was in the second, fifth and ninth years of life. Males comprised 63 per cent of the group and females 37 per cent. The incidence was highest in northern European nationalities. A history of diabetes in the family was obtained in 21 per cent of the children. The overfeeding of

carbohydrate, trauma and infections appeared to be excitive factors in a few instances. The sugar tolerance level did not fall in any case that was well controlled. There were five deaths from diabetic coma.

LEMASTER, Evanston, Ill.

THE SIGNIFICANCE OF HEMOPTYSIS. PORTER P. VINSON, J. South Carolina M. A. **30**:72 (May) 1934.

Hemoptysis is indicative of pulmonary disease and usually is a sign of tuberculosis, but there are many other causes of hemoptysis, which may be listed as follows: (1) bleeding from the gums, in which the blood is spit up in the early morning; (2) hemorrhage from the nose, in which the blood drains back into the pharynx and is expectorated; (3) ulcerative lesions in the nasopharynx; (4) rupture of the large vessels at the base of the tongue, which is considered rare; (5) chronic bronchiectasis and pulmonary abscess; (6) overstrain or violent exercise, as in swimming; (7) bronchial stricture, which may be associated with the presence of a foreign body or previous injury; (8) carcinoma or neoplasm; (9) hypostatic congestion of the lungs, which is usually associated with chronic heart disease; (10 mycotic diseases of the lungs, such as actinomycosis; (11) pneumonia, and (12) pulmonary infarction.

The importance of bronchoscopic examination is emphasized in bronchial stricture, neoplasm, abscess and the presence of a foreign body.

WESTON JR., Columbia, S. C.

HEART DISEASE PREVENTION VERSUS HEART SALVAGE. EDWARD I. BAUER, M. Clin. North America **17**:639 (Nov.) 1933.

Rheumatic infection is a generalized condition, with many portals of entry and many foci of infection distributed throughout the body as submiliary nodules. Cardiac involvement is not a sequel but a part of the disease. Tonsillectomy will not prevent heart disease or recurrent attacks. Infection may still occur through the tissues of the throat without lymphoid adnexa, and recurrences or relapses may occur from the virus in the submiliary nodules. Prophylaxis in rheumatic infection is largely a problem of public health—a problem of housing, sanitation, ventilation and heating. The task of instructing the patient in proper habits of living, exercise, diet and dress, is the direct obligation of the physician. For the rheumatic patient these factors are of supreme importance, since the prevention of heart disease consists largely in early recognition of the infection and careful regulation of all the activities of the patient. EUGENE SMITH, Ogden, Utah.

QUININE IN THE PNEUMONIAS OF INFANCY AND CHILDHOOD. MYER SOLIS-COHEN, M. Clin. North America **17**:787 (Nov.) 1933.

Solis-Cohen advocates the use of comparatively large doses of quinine early in the course of both lobar pneumonia and bronchopneumonia. His results have been favorable in shortening the course of the disease and especially in combating toxemia. He also claims that complications, such as heart failure, empyema, septicemia and meningitis, occur less frequently as a result of such treatment. The doses of quinine advised are: for persons 6 months of age or under, one or two doses of 5 or 10 grains (0.3 or 0.6 Gm.), followed by 2½ or 5 grains (0.16 or 0.3 Gm.) later, with increasing doses according to age. The drug is usually given by mouth in the form of the dihydrobromide. In case the stomach is intolerant, quinine and urea hydrochloride may be given by rectal suppository or by intramuscular injection. If the latter procedure is used, care must be taken to avoid injection into the subcutaneous tissue, else sloughing and necrosis of tissue may result.

EUGENE SMITH, Ogden, Utah.

ON CELIAC DISEASE. MAX EINHORN, M. J. & Rec. **138**:466 (Dec. 20) 1933.

The author reports five cases in which the condition had been diagnosed as celiac disease and in which the patients had received the usual celiac diets, without any improvement being noted. He states that he treated these patients by giving a full generous diet, making sure that they received enough of the different vitamins, and that all recovered and became normal.

In conclusion, he states that in his opinion celiac disease is frequently caused by diets insufficient in nutritive material or vitamins or in both and that the disease can be cured by the addition of these elements.

WILLIAMSON, New Orleans.

THE SCHILLING HEMOGRAM IN PEDIATRICS. HARRIS HOSEN, New Orleans M. & S. J. **86**:229 (Oct.) 1933.

At 6 years the normal blood count of a child approximates that of an adult. The count in infants averages from 12,000 to 15,000 cells, with lymphocytosis and neutropenia on differential count.

The author gives Schilling's sources for white blood cells: (1) granulocytes from bone marrow, (2) lymphocytes from lymphoid tissue and (3) monocytes from the reticulo-endothelial system. He then classifies the neutrophils, and divides the response of the blood stream to infection into three phases to interpret the prognosis. A clear exposition of the technic used in preparing the slides is given, together with illustrative reports of cases in children.

The author concludes:

1. The cases reported were selected at random from approximately three hundred and fifty patients.

2. The Schilling blood count proved to be far more valuable than the blood count based on the old Ehrlich classification.

3. The differential (Schilling) count proved far superior to the total leukocyte count.

4. In all cases of pyogenic infection the Schilling count equaled or substantiated the clinical findnigs.

5. In a great many cases the blood count proved far more valuable than the clinical picture.

6. In a majority of cases the response of the blood occurred earlier than the important clinical signs.

7. The Schilling hemogram proved to be invaluable when used in conjunction with clinical findings.

SMITH-FINE, Dallas, Texas.

DIVERTICULOSIS OF THE ALIMENTARY AND URINARY TRACTS. EDWIN BEER, New York State J. Med. **33**:907 (Aug. 1) 1933.

Diverticulosis has been found in all parts of both the alimentary and urinary tracts. It is only when diverticula become infected that their presence is suspected. A review of the subject is given. It is shown that diverticula are more common than was once thought. By modern methods, especially roentgenologic study, they can be detected and treated successfully.

AIKMAN, Rochester, N. Y.

COMMON DISEASES OF THE BONES AND JOINTS IN CHILDREN. WALTER STEFFEN, New York State J. Med. **33**:1031 (Sept. 1) 1933.

A review of common diseases of the bones and joints is presented in a symposium.

AIKMAN, Rochester, N. Y.

A Comparative Study of the Value of Tetrachlorethylene as a Means of Ultimate Control and Eradication of Hook-Worm Disease in Children. Harvey F. Garrison, South. M. J. **27**:24 (Jan.) 1934.

Statistics from laboratories of departments of health of the South, from physicians in private practice and from other well known authorities would indicate that, although the percentage of persons with hookworm has been greatly reduced within the last twenty years, the disease is still prevalent.

The results obtained with tetrachlorethylene, as compared with those following the use of oil of Chenopodium and carbon tetrachloride, by all who have had an opportunity to make any comparison, even under field conditions, would indicate the superiority of tetrachlorethylene.

Studies of the pharmacology, toxicology and therapeutic effects of tetrachlorethylene justify the conclusion that it is the safest, most economical and best treatment known for hookworm disease.

Schlutz, Chicago.

Immunizations and Vaccines. R. C. Farrier, West Virginia M. J. **30**:20 (Jan.) 1934.

This article is a brief review of the literature on the use of various vaccines, serums and bacterial vaccines for the prevention and treatment of certain diseases, together with some comments on the author's personal experience. There is no attempt to establish any new data of particular value, and no experiments are reported.

Shawkey, Charleston, W. Va.

The Acute Cerebral Complications of "Nephritis." George M. Lyon, West Virginia M. J. **30**:255 (June) 1934.

Acute glomerular nephritis (acute hemorrhagic or acute postinfectious nephritis) is the type of acute nephritis most frequently met with in children.

The term "cerebral complication" was used by Blackfan to describe the rather common group of symptoms consisting of vomiting, headache, dizziness, visual disturbance, convulsions and coma, which is frequently erroneously called uremia. This symptom complex is due not to the retention of nitrogenous end-products, but to the toxic factor responsible for the general condition. The special condition involved is edema of the brain. This complication is not proportionate to the amount of hematuria, the duration of the nephritis or the amount of nitrogenous products retained.

Relief has been obtained by the intravenous use of a 2 per cent solution of magnesium sulphate or a 25 per cent solution given intramuscularly.

In case of a rise of blood pressure, from 15 to 30 cc. of a saturated solution of magnesium sulphate should be given by mouth every four to six hours; this amount should be reduced by half when the blood pressure falls to normal and the cerebral symptoms are relieved. This amount should then be continued every eight to twelve hours. Fluids should be forced, and the patient should be fed a diet poor in salt.

In the presence of cerebral edema, high blood pressure, convulsions or coma, from 0.2 to 0.4 cc. of a 25 per cent solution of magnesium sulphate per kilogram of body weight should be given intramuscularly. If relief is not obtained, this dose should be repeated within two or three hours. In an emergency, a 2 per cent solution may be given intravenously. With either method the solution should be given by mouth, and fluids should be forced. The prognosis is favorable.

Shawkey, Charleston, W. Va.

Bronchiectasis. Francis C. Roles and Geoffrey S. Todd, Brit. M. J. **2**:639 (Oct. 7) 1933.

This interesting study does not lend itself readily to abstracting because of the description of technical procedures. It must be read to be fully appreciated.

Royster, University, Va.

CHRONIC INFLAMMATORY CONDITIONS SIMULATING PULMONARY TUBERCULOSIS. GEORGE JESSEL, Brit. J. Tuberc. **27**:69 (April) 1933.

Fibrosis in the lungs is a pathologic condition rather than a definite disease. The process proceeds in a manner common to healing elsewhere, viz., scar or fibrous tissue formation is followed by contraction or shrinkage of the adjacent parts. In chronic conditions of the bronchi there is a tendency toward destruction and weakening of the bronchial walls, resulting in bronchiectasis. The latter condition accounts for many cases of chronic disease of the chest, which is frequently confused with tuberculosis. Unlike tuberculosis, the onset of which is usually insidious, the beginning of chronic nontuberculous disease frequently coincides with a severe infection, such as measles, whooping cough or bronchopneumonia. Convalescence may be prolonged, with recurring colds and coughs. Râles may persist for some time and are usually evident during exacerbations. Bronchopneumonia may occur as an acute condition. In cases presenting such a history, in which the physical signs are largely found in the lower lobes and in which the sputum shows no tubercle bacilli, the presence of bronchiectasis may be expected with some confidence.

EUGENE SMITH, Ogden, Utah.

A STUDY OF ASTHMATIC AND RHEUMATIC CHILDREN WITH SPECIAL REFERENCE TO THE PHYSICAL TYPE. MATTHEW YOUNG, J. Hyg. **33**:29 (Nov.) 1933.

Greek medicine taught that individual predisposition was of primary importance in the genesis of disease. Interest in the constitutional aspect, which waned with the development of the medical sciences, is reviving. The physical form and the color of the hair and eyes have been considered important in the incidence of, and response to, disease, both bacterial and nonbacterial.

A series of anthropometric measurements were made on children attending the special clinic for asthma and for rheumatism of the Great Ormond Street Hospital for children of parents of means. A control group was made up from children attending clinics for trivial ailments. More than twelve hundred children between 6 and 12 years of age were measured. Thirty-one measurements, besides other observations, were made on each child. Careful comparison of the various indexes of measurement disclosed no appreciable difference between the children of the normal, asthmatic and rheumatic groups. Though the anteroposterior thoracic dimensions of the asthmatic group was slightly greater than for the other groups, this difference was considered a result of the disease. Asthma was more common in blonds than in dark-haired children.

JANNEY, Wauwatosa, Wis.

SUBCHRONIC HEMOLYTIC (ERYTHRONOCLASTIC) ANEMIA. W. C. SMALLWOOD, Proc. Roy. Soc. Med. **26**:1536 (Oct.) 1933.

A child admitted to the hospital at the age of 5 months was listless and irritable. The skin was waxy, with a café au lait pigmentation and numerous purpuric spots over the various parts of the body. The head was bosselated and the spleen and liver were enlarged. The results of examination of the blood and the blood counts are given in full.

WILLIAMSON, New Orleans.

SPRUE COMMENCING AT 11½ YEARS OF AGE. REGINALD MILLER, Proc. Roy. Soc. Med. **27**:113 (Dec.) 1933.

A boy, aged 13 years, had lived in Ceylon for six years, during which period he had kept well. In October 1931, he returned to England in excellent health and eating well. Six months later he began to complain of pain in the abdomen, with vomiting and diarrhea. He wasted considerably and became listless and irritable. The abdomen became very large, and he lost his appetite. Six months later he complained of a sore tongue. The condition was diagnosed as abdominal tuberculosis, but the patient showed the perversions of appetite and temperamental

difficulties that are seen in celiac disease. His stools, about two per day, were large and fatty. He was put on a strict diet containing the minimum of fat and in a short time showed marked improvement. A diagnosis of sprue was made, in spite of the patient's age, because of the condition of the tongue, the fatty diarrhea and the severe hyperchromic megalocytic anemia. The blood counts are given.

WILLIAMSON, New Orleans.

EXTREME HEPATOMEGALY IN AN INFANT. ROBERT HUTCHINSON, Proc. Roy. Soc. Med. **27**:118 (Dec.) 1933.

A case of extreme hepatomegaly in an infant, aged 4 months, an only child, is reported. On examination, the liver was found to extend from the costal margin to halfway between the umbilicus and the pubis. The spleen was not palpable. The results of examination of the blood, urinalysis and biochemical investigations are given in the report and a photograph of the patient is included.

WILLIAMSON, New Orleans.

THE PERIPHERAL CIRCULATION IN ACUTE LOBAR PNEUMONIA. C. BRUCE PERRY, Quart. J. Med. **3**:273 (April) 1934.

The author reports observations on the behavior of the small vessels of the skin in twenty-six patients with lobar pneumonia. Throughout the course of the disease observations were made on the color of the skin, the blood pressure, the response of the vessels of the skin to histamine, to stroking and to epinephrine and, finally, the back pressure on the circulation required to obliterate the blanched area produced by epinephrine.

Impaired efficiency in the contractibility of the capillaries at the height of the disease was observed. It was found that the recovery of the capillaries is slow and not immediately affected by the crisis, that a part of the circulatory failure in lobar pneumonia is due to impairment in the efficiency of the small blood vessels and that the blood pressure is raised rather than lowered during the acute phase of the disease.

BRADFORD, Rochester, N. Y.

CHRONIC PULMONARY CATARRH AND FIBROSIS IN SCHOOL CHILDREN. H. STANLEY BANKS and J. H. WEIR, Tubercle **14**:385 (June) 1933.

The differentiation of tuberculous from chronic nontuberculous pulmonary disease in children is an important problem confronting authorities in sanatoriums. This article is based on the careful study of a consecutive series of one hundred children referred for admission because of pulmonary tuberculosis. Eventually these children were classified as follows: group 1, those with chronic pulmonary catarrh, sixty-six; group 2, those with chronic bronchitis, twenty-three; group 3, those suffering from malnutrition and debility from causes other than respiratory, ten, and group 4, those suffering from pleurisy with effusion, one. Of the first group, in which the condition was designated as "chronic pulmonary catarrh," "pulmonary fibrosis," etc., thirty-three children reacted to tuberculin, and roentgenograms in many cases showed evidences of a primary infection. The features which were common to all were a chronic or recurrent basal pulmonary lesion, the onset of which could be dated from an acute respiratory episode many years or months before admission. The symptoms closely resembled those of phthisis in the adult, but there was no continuous loss of weight and health. The physical signs in the chest were found at the base of one or both lungs and consisted of changes in the respiratory murmur and localized râles and rhonchi. Commonly, the fingernails were spooned or clubbed. The characteristic roentgen findings were: clear fields in the upper part of the lung associated with marked increase in linear striae and diminished translucency from the hilus to the diaphragm. In severe cases flattening and irregularity of the outline of the diaphragm and mottling in the lower zone suggestive of dilated bronchioles were often present. Repeated exami-

nation for tubercle bacilli by all methods gave negative results. "The early pathology of this condition is that of bronchiectasis, viz., a catarrhal infection of the bronchiole wall sufficiently acute or prolonged to prevent complete repair, leaving it thinned, stretched, infiltrated with round cells and readily subject to acute flare-ups with each added infection. It appears to be an intermediate stage of bronchiectasis itself."

Of the twenty-three cases designated as cases of chronic bronchitis, in fourteen there was a reaction to tuberculin. Clinically, the condition somewhat resembled those of the preceding group, but the signs in the chest tended to be general rather than basal in their distribution, and roentgen signs were negative or showed well marked bronchial striation without loss of translucency. The history of acute onset with recurrences was not so clear as in group 1, and gross nasopharyngeal sepsis was almost invariably present.

In nine of the ten cases in group three there was a reaction to tuberculin, but signs in the chest were absent, and examination for tubercle bacilli gave negative results. These patients, however, exhibited various forms of sepsis, e. g., chronic otitis, rhinitis, pyelitis and other infectious processes. There was no evidence of tuberculous disease, other than obsolescent primary infection.

In the one case of pleurisy with effusion there was a strongly positive Pirquet reaction, and a roentgenogram showed a calcified Ghon focus.

The authors believe that a diagnosis of pulmonary tuberculosis should not be made in children between the ages of 3 and 12 years, except when tubercle bacilli are found in the sputum, the contents of the stomach or the feces or unless definite tuberculous infiltrations are shown on x-ray films.

EUGENE SMITH, Ogden, Utah.

PRIMARY HYDATID CYST OF THE MYOCARDIUM. L. MORQUIO, Arch. de méd. d. enf. **37**:90 (Feb.) 1934.

The case of a boy, aged 11, who resided in a country district near Montevideo, is reported. On admission to the hospital it was found that he had been suffering from violent headache, accompanied by vomiting and constipation; for a month and for twelve days prior to admission there was photophobia with strabismus.

Examination showed, in addition, slight rigidity of the neck, a positive Kernig sign and pronounced mental confusion; the spinal fluid, however, was normal, as were the blood and urine. The cutireaction for tuberculosis was negative. Within ten days the fundi revealed markedly dilated vessels and papilledema; the frontoparietal sutures became separated, and an area of softening developed on the right parietal suture. At this time ventriculography was carried out, and roentgenograms revealed a tumor of the left ventricle invading the area of the right ventricle. The patient continued to fail and died at the end of five weeks. Autopsy revealed a primary echinococcus cyst of the left side of the heart, rupturing into the ventricle, with nine multiple metastatic cysts of the brain and two of the spleen.

The author could find but twenty-four similar cases reported in the literature, all of them being in older persons.

AMESSE, Denver.

A CASE OF SENILE DWARFISM, OR PROGERIA. Y. POUZIN-MALÈGUE, Bull. Soc. de pédiat. de Paris **30**:685 (Dec. 20) 1932.

A boy, 9½ years old, presented the picture of a senile dwarf. He weighed 13.7 Kg. (30.1 pounds) and was 107 cm. (42.1 inches) tall. The genitalia were markedly underdeveloped. The intelligence was normal for his age. He had weighed 1,000 Gm. (2 pounds and 3 ounces) at birth, which occurred after a full term pregnancy. At 1 year he was walking and weighed 3 Kg. (6 pounds and 9 ounces). Roentgen examination of the skeleton showed the bones to be small, corresponding to the diminutive stature; the epiphyses and diaphyses were nowhere consolidated. During the time he was observed the period of best growth followed a series of ultraviolet ray treatments. Dryness and pigmentation of the skin, which

were present, as well as some asthenia, cleared up after he had been given suprarenal extract; whether the latter had any specific therapeutic effect is impossible to ascertain.

BENJAMIN, Montreal, Canada.

SINUS THROMBOSIS IN A DYSTROPHIC INFANT AFTER PUNCTURE OF THE LONGITUDINAL SINUS. AXENTE IANCOU, Bull. Soc. de pédiat. de Paris **30:** 702 (Dec. 20) 1932.

A number of cases of death after puncture of the longitudinal sinus in infants are reported, as well as a series of cases in which the administration of various fluids by this route was followed by no untoward sequelae. Observations at necropsy of thrombosis of the superior longitudinal sinus in a boy, aged 2½ months, whose sinus had been punctured one month and ten days previously, are reported. Convulsions marked the onset of neurologic symptoms ten days before death. Apparently, only one puncture was performed, and it is not stated whether blood was withdrawn or whether intravenous treatment was given. This case of sinus thrombosis occurred in a series of one hundred and fifty cases in young infants in which puncture of the superior longitudinal sinus was performed.

BENJAMIN, Montreal, Canada.

PULMONARY ABSCESS CURED WITH EMETINE. G. PAISSEAU and G. PATEY, Bull. Soc. de pédiat. de Paris **31**:97 (Feb. 21) 1933.

A girl, 5 years of age, had been ill for about fifteen days. Physical examination revealed abnormal findings over the upper lobe of the right lung. A roentgenogram of the chest showed the presence of an abscess with a fluid level in this region. She was given seven injections of 2 cg. of emetine each at intervals of two days. After a week she was much improved, and after another week she was cured. This was confirmed roentgenologically. Examination of the blood showed no leukocytosis; monocytosis and 4 per cent eosinophils were found. The stools were examined for the presence of amebae, but none was found. The patient's father had been in the Orient for a considerable time before this child was born; he gave no history of having had amebic dysentery, and his stools showed no amebae. It is believed that the father's sojourn in a country where amebic dysentery is known to be endemic and the favorable therapeutic result following the administration of emetine permit of a diagnosis of amebic abscess of the lung.

BENJAMIN, Montreal.

THE CONGENITAL FACTOR IN BRONCHIECTASIS OF INFANTS. P. LEREBOULLET, Paris méd. **1**:156 (Feb. 17) 1934.

The author reports four cases of bronchiectasis in infants, illustrated with roentgenograms in which, following the injection of iodized poppy-seed oil 40 per cent, multiple cysts were shown, with a lobular or pseudolobular localization that gave every evidence of congenital origin. He calls attention to the fact that many of these cases may be congenital. In regard to the treatment, he believes that a medical regimen by posture should be the first procedure. If this gives no results, drainage by bronchoscopy should be used, and, finally, some good results are obtained surgically by phrenectomy.

SANFORD, Chicago.

MENTALITY OF INFANTS WITH CELIAC DISEASE. H. ELIAS and M. SCHACHTER, Progrès méd., Feb. 17, 1934, p. 286.

The parents of children with celiac disease often show neurasthenia and mental debility. There is a history of frequent digestive upsets and a faulty appetite. This may have some bearing on the child's heredity. In general, these children are of reduced intelligence and are apathetic and slow to respond. They are often catatonic. As they improve, the appetite is very capricious, and there are spells of

anorexia and of eating bizarre substances, such as earth or paper. Later, they show signs of latent tetany. The musculature is relaxed and atonic. Neurologic examination shows some reflexes increased and some absent.

SANFORD, Chicago.

A CASE OF CONSTITUTIONAL HYPERSPLENOMEGALIA. D. ANGARANO, Pediatria **41**:922 (July 1) 1933.

A case of hypersplenomegalia is reported in which the clinical picture resembles closely that of Banti's disease, but in which several pathognomonic characteristics are lacking. The author concludes that only on the basis of the doctrine of idiopathy is it possible to explain the pathogenesis, referring to the fact that it would be necessary to examine constitutional factors, which have an important bearing also on the pathogenesis of all types of cirrhoses, which in turn bear a relation to certain conditions due to endocrine dysfunction. SIGNORELLI, New Orleans.

STILL-CHAUFFARD DISEASE: CLINICAL AND ANATOMIC PATHOLOGIC STUDY. E. BENEDETELLI, Pediatria **42**:159 (Feb. 1) 1934.

The author gives a brief description of this disease and reports a case which he observed from its beginning and followed up for one year. Tuberculous infection could be thoroughly excluded in the case reported, which suggests that tuberculosis should not be considered, as it is by some authorities, as an etiologic or predisposing factor in this disease. The etiology in the author's case remains obscure, although numerous researches were carried on.

Biopsy of three lymph glands demonstrated only a chronic irritative condition. Several attempts at therapy were without result. SIGNORELLI, New Orleans.

ETIOLOGY OF BRONCHIECTASIS. PAOLO JACCHIA, Pediatria **42**:173 (Feb. 1) 1934.

The author expresses his opinion that some cases of congenital bronchiectasis are dependent on alterations of the germ plasm and attempts to confirm this opinion by reporting a case of a boy, 13 years of age, who exhibited deformity of the external ear, occlusion of the meatus of the right ear and nearly asymptomatic bronchiectasis in the lower lobe of the right lung. An interpretation of congenital origin is given because of the negative history and because of the roentgen findings, which consisted in enlarged and distorted bronchi.

SIGNORELLI, New Orleans.

ANEMIA APLASTICA GRAVIS. J. M. MACERA, M. H. DI FIORI, B. MESSINA and M. VAQUER, Arch. argent. de pediat. **4**:336 (May) 1933.

The authors report a case of this comparatively rare blood picture in a girl, aged 10 years.

Intense anemia was present. There was no anisocytosis or poikilocytosis. There was no polychromatophilia or manifest leukopenia. Immature forms of cells were completely absent from the circulating blood. Immature forms of white cells were found in the medulla of some of the bones. There was no decrease of blood platelets. The retina showed hemorrhages, but there were none in the peripheral parts of the body. The gastric juice was normal, and intestinal parasites were not found. SCHLUTZ, Chicago.

PRIMARY SARCOMA OF THE LUNG IN AN INFANT AGED TWENTY-ONE MONTHS. M. J. DEL CARRIL, M. J. VERGNOLLE and B. PAZ, Arch. argent. de pediat. **4**:513 (July) 1933.

The duration of the illness in the case reported, from the onset to the fatal termination, was slightly more than one month. Slight cough and increasing

dyspnea were pronounced symptoms. The tumor filled almost the entire right side of the chest and extended over into the left side. There was extensive mediastinal involvement. The tumor was a sarcoma of the polymorphous cellular type.

SCHLUTZ, Chicago.

HYPERTROPHY OF THE THYMUS IN A CHILD AGED THREE YEARS. J. C. NAVARRO and F. DE ELIZALDE, Arch. argent. de pediat. **4**:578 (Aug.) 1933.

This case is remarkable on account of the age of the child. Enlargement of the thymus is unusual beyond infancy. There were marked asthmatic symptoms and definite primary tuberculous infection.

Two exposures to the roentgen rays at intervals of a few weeks caused the entire disappearance of the shadow and relief of all the manifest symptoms.

SCHLUTZ, Chicago.

A CASE OF PURULENT ASCITES. S. CARNEIRO, Arch. de pediat., Rio de Janeiro **7**:631 (March) 1934.

A child, 1 year old, presented an enlarged abdomen containing fluid. The mother was syphilitic, but the child had no stigmas. Two hundred cubic centimeters of fibropurulent fluid was drawn off; this did not cause tuberculous lesions when injected into a rat. For this reason the author believes that the ascites was syphilitic in origin, and that the child was secondarily infected by organisms from the gastro-intestinal tract.

SANFORD, Chicago.

MYELOID LEUKEMIA AND VON JAKSCH-LUZET ANEMIA IN AN INFANT. JULIO LORENZO Y DEAL and HECTOR MOURIGAN, Arch. de pediat. d. Uruguay **4**:391 (Sept.) 1933.

The authors report a case of myeloid leukemia in an infant, aged 14 months. This condition is not as infrequent in young infants as is generally believed. The differential diagnosis between this primary blood disease and the von Jaksch-Luzet type of anemia is difficult at times. The outcome is not necessarily fatal.

SCHLUTZ, Chicago.

FOREIGN BODY IN THE STOMACH. MARCOS DIAZ SARDINA, Bol. Soc. cubana de pediat. **5**:75 (March) 1933.

If the object swallowed is rounded and without sharp edges or points, it is safe to adopt an expectant attitude, regardless of its size. It generally will traverse the digestive tube safely. If the object is sharp, pointed or with cutting edge and small, it is safe to adopt an expectant attitude. Interference is necessary only if alarming symptoms arise. Proper diet and antispasmodic remedies must be given. If the aforementioned objects are of considerable size, it is unsafe to wait for their possible passage. Gastrostomy should be performed. This is the most certain and safe procedure.

SCHLUTZ, Chicago.

THE CONGENITAL ADIPOSOGENITAL SYNDROME OF BIEDL. A. CARRAU and J. C. ETCHEVERRY, Pediatría españ. **22**:495 (Aug.) 1933.

This condition may be present at birth and is usually due to a congenital lesion. It is generally accompanied by other stigmas, such as polydactylism and pigmented retinas. There may be mental retardation and deformity of the head. Rectal anomalies and various articular subluxations are often present. The genitalia are always extremely small.

The authors report a case in a child 4 years old. The patient showed gross obesity. Subluxation of the joints of the elbow and genu valgum were present.

There were six fingers on each hand and six toes on each foot. Genital hypoplasia was pronounced. Vision was very defective, and there was a low grade of intelligence. The sella turcica was markedly small.

The authors recommend the early use of pituitary gland and thyroid extract in these cases. They also advocate the general use of antisyphilitic treatment. A rigid reducing dietetic regimen is always indicated. SCHLUTZ, Chicago.

GLYCOGENOSIS. P. KIMMELSTIEL, Beitr. z. path. Anat. u. z. allg. Path. **91**:1, 1933.

The condition which the author portrays was first described under the name glycogenic hepatonephromegaly by von Gierke in 1929 (*Beitr. z. path. Anat. u. z. allg. Path.* **82**:497, 1929); two additional cases were reported by Putschar (*Beitr. z. path. Anat. u. z. allg. Path.* **90**:222, 1932). The author's case is the fourth recorded example of this condition, for which he prefers the name "glycogenosis." A child died of acute pharyngitis and bronchopneumonia; the age at death is not stated in the brief clinical summary. Enlargement of the abdomen was noticed by the mother when the child was between 3 and 4 weeks old. At necropsy, the liver extended below the level of the umbilicus and weighed 1,600 Gm. Each kidney weighed 45 Gm., and, as was true in Putschar's cases, was much less enlarged than in von Gierke's case. The liver, cardiac muscle, voluntary muscle and brain contained large quantities of glycogen; the kidneys contained a smaller amount, situated chiefly in the epithelium of the straight tubules. The glycogen did not disappear as rapidly from the liver after death as is usually the case. Although the glycogen of the liver yielded as large a proportion of dextrose on acid hydrolysis as did pure glycogen or the glycogen of normal dog's liver, it yielded a definitely smaller proportion when subjected to diastatic fermentation. The pancreatic islets were histologically normal, with the exception of a few that were somewhat enlarged. The two previous observers sought the explanation of the condition in decreased glycogenolytic activity of the liver. In view of the unequal distribution of the glycogen, especially in a single organ like the brain, Kimmelstiel does not accept this suggestion. He postulates a disturbance of carbohydrate metabolism that leads to the formation of a heterotypical form of dextrose, which is polymerized into a form of glycogen that is not readily split by the normal diastatic enzyme. O. T. SCHULTZ. [ARCH. PATH.]

CONGENITAL NEUROFIBROMATOUS MACROGLOSSIA. H. MÜLLER, Centralbl.f. allg. Path. u. path. Anat. **57**:55, 1933.

This rare condition was found in the body of a boy, 6 years old, who was mentally retarded. Over the entire body there were numerous nevi, some finely and some coarsely pigmented. There was also a tumor of the right side of the dorsal third of the tongue. In the tongue the papillae were enlarged, and scattered in the muscle were pinhead-sized nodules and strands of gray-yellow tissue. The nodules contained medullated nerves in their central parts, but no ganglion cells. The muscle about them was loose. RUKSTINAT. [ARCH. PATH.]

DEAFNESS IN OSTEOPSATHYROSIS. R. SCHNEIDER, Ztschr. f. Laryng., Rhin., Otol. (Teil 1: Folia oto-laryng.) **24**:362 (Nov.) 1933.

Schneider discusses the syndrome of osteopsathyrosis, blue sclerotica and deafness, which has recently been recognized clinically as a triad of symptoms of hereditary nature. The osteopsathyrosis, the deafness or both may be lacking in some cases, but the symptom of blue sclerotica is practically never absent. The deafness becomes manifest at the time of puberty or earlier in the form of conduction deafness, to which labyrinthine deafness is usually added later. The decrease in hearing is progressive; it is accompanied by severe tinnitus and sometimes ends in total deafness. The deafness is regarded as otosclerotic by most authors. The author has observed this triad of symptoms seven times in the course

of one year. He calls attention to the fact that the occurrence of blue sclerotica may explain the nature of an incipient or uncharacteristic deafness or may even lead to the discovery of a disturbance in hearing before it is noticed by the patient and may thus be of significance in determining the choice of a profession.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

FAMILIAL OCCURRENCE OF LEUKEMIA. SVEND PETRI, Acta path. et microbiol. Scandinav. **10**:330, 1933.

The literature is reviewed, and thirty-three cases of familial leukemia are described, of which eleven are beyond doubt. The lymphatic type occurred in twenty-two instances. There was an average of three cases in a family. The author adds a report on chronic lymphatic leukemia in two brothers. There is no evidence of hereditary transmission of leukemia, although there is some endogenic factor associated. The presence of infection or of a common external agent could not be ruled out. The possibility of mere coincidence in familial leukemia must be considered. Lymphatic leukemia occurred in 85 per cent of related persons, while myelogenous leukemia occurred in nonrelated persons.

JACOB KLINE. [ARCH. PATH.]

Nervous Diseases

THE TREATMENT OF CHOREA BY INDUCED FEVER. LUCY PORTER SUTTON and KATHERINE G. DODGE, J. Pediat. **3**:813 (Dec.) 1933.

In this report the results since 1930 of treating 150 children with chorea by means of daily intravenous injections of typhoid-paratyphoid vaccine are compared with the results obtained by treating 150 patients with chorea by other methods prior to 1930.

Sufficient doses of vaccine were used to insure a daily temperature of 104 F. or more, and maintenance of the fever for as many hours as possible. Treatment was given daily until all signs of chorea disappeared. In the patients receiving vaccine the average duration of the attack in mild cases was 5.72 days; in moderate cases, 8.56 days, and in severe cases, 15.8 days, as compared with a duration of 27.4, 44 and 62.4 days for similar groups not receiving vaccine. The authors conclude that fever therapy is a satisfactory method of treatment of chorea.

LEMASTER, Evanston, Ill.

SYMPATHECTOMY IN ANTERIOR POLIOMYELITIS. E. D. TELFORD and J. S. B. STOPFORD, Brit. M. J. **2**:770 (Oct. 28) 1933.

This is a discussion of the dermal changes and circulation in a limb paralyzed from poliomyelitis, with a report of three cases in which lumbar sympathectomy was performed, with marked improvement. ROYSTER, University, Va.

TREATMENT OF CHOREA BY INDUCED PYREXIA. J. W. CHEETHAM, Brit. M. J. **2**:815 (Nov. 4) 1933.

This article is an account of the treatment of chorea by induced hyperpyrexia by means of typhoid vaccine. The author concludes that the treatment shortens the duration of choreic movements. It does not prevent recurrence and appears to have no beneficial action on rheumatic carditis. ROYSTER, University, Va.

TREATMENT OF CHOREA BY INDUCED PYREXIA. HUXLEY FISH, Brit. M. J. **2**:816 (Nov. 4) 1933.

The author discusses the treatment of chorea by induced pyrexia by means of typhoid vaccine and reports a case. The three types that are suitable for treatment by induced pyrexia are: (1) cases in patients with no signs of cardiac rheumatism

who show little improvement after four weeks in bed in an institution, (2) cases in patients with slight cardiac rheumatism in whom a period of rest longer than four weeks in proportion to the severity of the cardiac lesion has produced little improvement and (3) cases of choreic relapse in which the previous attack or attacks have been of long duration (the heart again being only slightly affected).

ROYSTER, University, Va.

POLIOMYELITIS. F. M. R. WALSHE, Brit. M. J. **2**:1197 (Dec. 30) 1933.

The author stresses the assumption that poliomyelitis is primarily a nerve infection and has no real preparalytic stage. What is supposed to be the preparalytic stage is merely the stage before the injury has gone far enough in the nerve to produce paralysis and not the stage before the nerve is affected. Then follows a general discussion of the evidence for and against the use of convalescent serum, with a brief conclusion that at present nothing is known of benefits following its use. The suggestion follows, however, that active immunity may be possible in the near future.

ROYSTER, University, Va.

THE BEARING OF RECENT WORK ON CERTAIN ASPECTS OF POLIOMYELITIS. J. PURDON MARTIN, Brit. M. J. **2**:1200 (Dec. 30) 1933.

This article consists in a general discussion, review and summation of the more recent work on the subject of poliomyelitis, with special reference to certain phases of this work.

ROYSTER, University, Va.

A CONTRIBUTION TO THE GENETIC STUDY OF MENTAL DEFICIENCY. L. S. PENROSE, Brit. M. J. **1**:10 (Jan. 6) 1934.

A case is reported in which a feebleminded brother and sister mated and produced offspring, one of which died early; the other two are apparently mentally normal.

ROYSTER, University, Va.

HEREDITY, A MINOR FACTOR IN MENTAL DEFICIENCY. CHARLES MCNEIL, Brit. M. J. **1**:584 (March 31) 1934.

The author reviews some of the literature, particularly the analysis of Dr. John Thomson, and adding to this his own observations arrives at the following conclusions:

A study of 1,000 cases of mental deficiency, constituting a large and representative sample of the condition as it occurs in the population, was carried out by a physician whose experience in the subject was extensive and whose reputation for clinical accuracy was high.

In the great majority of the cases (85 per cent) the condition was congenital, and in a large majority (65 per cent) it was antenatal in origin.

In a large majority (two-thirds) it was the result of nonhereditary morbid processes acting before, during and after birth.

In only a small fraction (0.4 per cent) was mental defect known to be produced by the mechanism of mendelian inheritance.

In a larger group (one third of the aggregate) an important influence of heredity may be accepted for cases in which the children were born of defective parents. These cases, however, form only a small minority of this group. In the great majority, when the parents were of normal mind the influence of heredity was uncertain and obscure.

The general conclusion appears to be that heredity plays a very small part in the production of congenital mental deficiency, and that its influence in this respect has been greatly exaggerated.

ROYSTER, University, Va.

FAMILIAL FORM OF DIFFUSE PERIAXIAL ENCEPHALITIS. G. HEUYER, C. VOGT and M. ROUDINESCO, Arch. de méd. d. enf. **37**:278 (May) 1934.

The disorder commonly known as Schilder's disease was described by Pierre Marie and Foix in 1913 as centrolobar cerebral sclerosis; since that time reports of numerous observations have been published. In France, particularly, the familial types of the disease have not been stressed, but many reports of cases appear in the literature of other continental states. In some of these cases the condition bears a striking resemblance to amaurotic family idiocy. The authors present complete clinical histories in two cases, those of sisters aged 2 and 4, with comments on the neurologic syndrome and its etiology.

AMESSE, Denver.

POLIOMYELITIS AFTER LUMBAR GANGLIONECTOMY. GERTRUDE HERZFELD, Tr. Edinburgh Med.-Chir. Soc., 1933, p. 172; in Edinburgh M. J., September, 1933.

Because of blueness, coldness and trophic sores of the legs in a boy after arthrodesis for drop foot due to poliomyelitis, resection of the second, third and fourth lumbar ganglions was performed. Within the following two months the temperature of the legs became normal. Herzfeld expresses the hope that there may be further benefit by increased growth to compensate for the shortening of the paralyzed limb.

NEFF, Kansas City, Mo.

POLIO-ENCEPHALITIS. LEWIS THATCHER, Tr. Edinburgh Med.-Chir. Soc., 1933, p. 174; in Edinburgh M. J., September, 1933.

A boy, aged 2 years, with a characteristic history and flaccid paralysis of the right leg, was found to have the following features, which are unusual in poliomyelitis: There was a marked degree of retraction of the head, with opisthotonos, with periods of intermission. The spinal fluid was turbid. The cells numbered only about 13 to the high power field; polymorphonuclears and mononuclears were present in equal numbers, but there were no organisms. The paralysis is all that remained after the illness, which subsided within ten days.

NEFF, Kansas City, Mo.

MICRENCEPHALY. EDITORIAL, J. Neurol. & Psychopath. **14**:61 (July) 1933.

The author comments on the literature and tendencies in the study of microcephalus.

JAHR, Omaha.

NEUROLOGICAL ABNORMALITIES: THEIR OCCURRENCE AND SIGNIFICANCE AS ILLUSTRATED BY AN EXAMINATION OF 500 MENTAL DEFECTIVES. R. G. GORDON, R. M. NORMAN and R. J. A. BERRY, J. Neurol. & Psychopath. **14**:97 (Oct.) 1933.

Five hundred certified mental defectives, aged from 5 to 41 years, 289 of whom were females and 211 males, were divided into two groups: Group 1 consisted of patients with high grade amentia with an intelligence quotient of 50 and above, but considerably less than normal (46 males and 121 females). Group 2 consisted of patients with low-grade amentia with an intelligence quotient below 50 (165 males and 168 females). Neurologic examination was carried out on all 500 patients. Special attention was paid to the proprioceptive and exteroceptive sensibilities, central coordinations, effector mechanisms and other nerve phenomena usually associated with manifestations of nervous disease. Tics and uncoordinated movements, convulsions, tremors and paralyses were also noted.

Charts and graphs representing the results of these studies are submitted, with the conclusion that mental defectives of all grades are subject to abnormalities of the nervous system. The abnormalities with few exceptions are due to failure of the nervous system to attain a development adequate to the performance of its intricate functions.

JAHR, Omaha.

THE PROPRIETY OF DIAGNOSTIC LUMBAR PUNCTURE IN INTRACRANIAL HYPERTENSION. W. F. SCHALLER, J. Neurol. & Psychopath. **14**:116 (Oct.) 1933.

One hundred and three cases of increased intracranial pressure due to various diseases are analyzed from the standpoint of danger from spinal puncture. The author supports the contention that danger of herniation due to spinal tap is exaggerated. In this series there were four deaths, two of which can be excluded as due to properly performed diagnostic punctures; two may or may not have been determined by punctures. There was no experimental or clinical evidence of wedging of the contents of the posterior fossa into the foramen magnum following spinal tap in open craniospinal pathways. Herniation can, however, be conceived of as an expression of general cerebral edema and may be due to changes in intracranial pressure, vasomotor paralysis and shock from different causes.

JAHR, Omaha.

INFLUENZAL MENINGITIS. H. STANLEY RODGERS, Proc. Roy. Soc. Med. **26**: 1375 (Aug.) 1933.

A boy, 2 years of age, was admitted to the hospital, having suffered from fever and vomiting for over a week. The fever continued, and lumbar puncture was performed. The fluid was turbid under pressure and contained a bacillus of the influenza group. Slight hydrocephalus developed and some stiffness of the neck, which persisted; later he suffered from a jacksonian fit (right side) which left him with right hemiplegia. A full report of examination of the cerebrospinal fluid is included.

WILLIAMSON, New Orleans.

TUMOR OF SPINAL CORD. F. A. R. STAMMERS, Proc. Roy. Soc. Med. **26**:1543 (Oct.) 1933.

A case of tumor of the spinal cord in a girl, aged 8 years, is reported. The patient was admitted to the hospital complaining of (1) pains in the back, (2) paralysis of the legs and (3) incontinence of the urine and feces. About six months previously she had complained of pain in the buttocks and stiffness of the back, which were treated as a rheumatic condition. Laminectomy revealed a tumor of the cauda equina, which the pathologist reported to be an ependymoma.

WILLIAMSON, New Orleans.

SEVERE EPILEPSY, COMPLETELY ALLEVIATED BY ENCEPHALOGRAPHY. J. M. SMELLIE, Proc. Roy. Soc. Med. **26**:1544 (Oct.) 1933.

A boy was admitted to the hospital suffering from convulsions of only a few weeks' duration. They were of petit mal type and were frequent. Lumbar puncture was performed; 55 cc. of cerebrospinal fluid was removed, and 40 cc. of air was introduced. The patient has remained perfectly well since. There have been no fits, although he now appears to be somewhat mentally defective.

WILLIAMSON, New Orleans.

TUBERCULOMA OF THE OCCIPITAL LOBE: REMOVAL; RECOVERY. F. A. R. STAMMERS, Proc. Roy Soc. Med. **26**:1544 (Oct.) 1933.

A child aged 11 years complained of headache and vomiting, which the parents thought were due to an accident eighteen months previously. Examination of the eyegrounds showed optic neuritis of 2 diopters. A diagnosis of cerebral tumor or abscess was then made. On passing the needle through a trephine hole toward the posterior horn of the right lateral ventricle (in order to perform ventriculography), a hard tumor was encountered. A parieto-occipital bone flap was made, and the tumor mass was removed. The child made a good recovery.

WILLIAMSON, New Orleans.

SEVERE EPILEPTIFORM CONVULSIONS: CONSIDERABLE IMPROVEMENT FOLLOWING ENCEPHALOGRAPHY. J. M. SMELLIE, Proc. Roy Soc. Med. **26**:1545 (Oct.) 1933.

A case of severe epileptiform convulsions in a child aged 5 years is reported. The patient was greatly relieved after encephalography was performed.

WILLIAMSON, New Orleans.

PROGRESSIVE FAMILIAL LEUKODYSTROPHIES. L. VAN BOGAERT and I. BERTRAND, Rev. neurol. **2**:249 (Aug.) 1933.

Several communications have appeared dealing with familial instances of a type of cerebral sclerosis allied to Schilder's disease. The names of Krabbe, Scholz and Ferraro are particularly associated in this regard, though Curtius presented the most extensive genetic study. Van Bogaert and Bertrand report the occurrence of the condition in two children of one family and in two of five children of another, while epilepsy, hemiplegia and optic atrophy occurred in several cousins. The clinical features are progressive blindness and rigidity, with pseudobulbar disturbances and indications of partial decerebration; reflex grasping is common. Pathologically, atrophy of the cerebral white matter is striking, and there is marked release of fat, with the formation of compound granule cells. The symmetry of the lesions is always almost perfect. There are evidently formes frustes, as indicated clinically in other cases. Moreover, dependent on the localization, one can find all types, from a pure pyramidal to a pure extrapyramidal process.

FREEMAN, Washington, D. C. [ARCH. NEUROL. & PSYCHIAT.]

FIRST CEREBELLAR SIGNS IN TUMORS OF THE CEREBELLOPONTILE ANGLE. HETEROLATERAL CEREBELLAR SYNDROME WITH EXTRAPYRAMIDAL PARKINSONISM DUE TO CEREBELLAR OVERFUNCTION. K. HENNER, Rev. neurol. **2**:377 (Sept.) 1933.

In a series of twenty-one proved and suspected cases of tumor of the cerebellopontile angle, Henner encountered the following peculiar syndrome on four different occasions: Whereas on the side involved there was usually considerable dyssynergia with other common cerebellar signs, on the opposite side there was some indication of catalepsy, as well as sudden arrest of the rebound phenomenon, limitation of the swing following the patellar reflex and sluggish and rather rigid voluntary movements of the hand. In certain cases even plasticity and hypometria have been found on the opposite side, with increase of the simple postural reflexes. But in no case was there the actual cogwheel phenomenon. In six other cases one or more of the preceding symptoms were present in addition to the classic cerebellar signs on the side of the tumor. Henner draws the conclusion that the parkinsonian syndrome may be due to overfunction of the cerebellum, which now lacks its normal restraint. Certain other examples of hyperfunction of the cerebellum leading to rigidity and akinesia have been reported, and in some instances primary overfunction of the cerebellum may apparently be succeeded by characteristic hypofunction, with the classic cerebellar signs.

FREEMAN, Washington, D. C. [ARCH. NEUROL. & PSYCHIAT.]

VARIATION OF THE OCULOCARDIAC REFLEXES IN CHILDREN FOLLOWING THE DIETETIC TREATMENT OF GERSON. GIAN CARLO BENTIVOGLIO, Pediatria **41**: 1457 (Dec. 1) 1933.

The author studied thirteen normal children between the ages of 5 and 12 years, observing strict caution and rigorous technic. He noted the oculomotor reflexes both during, and at the end of, treatment according to the dietetic method of Gerson. The treatment was continued over a period of from one to two months. In the majority of his cases the author observed a moderate accentuation of the positivity of the reflexes.

Study of the blood chemistry, which was carried out with the foregoing observations, demonstrated: a coexisting diminution of the potassium content of the serum; a slight, though constant, increase of the potassium and phosphorus as well as of the cholesterol in the total blood, and a minute modification of the calcium content, which was more evident in the direction of an increase in the total blood.

The author concludes that it is possible that a certain stimulating influence results from the dietetic treatment of Gerson, which is exhibited more directly on the activity or tone of the parasympathetic function. Further researches extended to cover other organovegetative reflexes may result in a more definite and more complete understanding of the relations here reported as existing between the Gerson dietetic management and the neurovegetative system.

SIGNORELLI, New Orleans.

CLINICOSTATISTICAL OBSERVATIONS ON SYDENHAM'S CHOREA. ELIO ZAMBRANO, Pediatria **41**:1495 (Dec.) 1933.

The author gives a complete review of the various theories concerning the etiology and pathogenesis as well as the anatomic and pathologic considerations of Sydenham's chorea. He also reports his own observations in connection with one hundred and ninety-six cases seen in the Royal Pediatric Clinic in Naples from 1914 to 1932 and discusses the relationship between chorea minor and other infections, especially rheumatism and syphilis. To these two diseases, as well as other infective factors, either hereditary or constitutional, he attributes the distinct value of predisposition.

He concludes that chorea minor is an infectious disease caused by a germ or a specific virus, which attacks especially children during the period of infancy and late infancy, females being afflicted more frequently than males; the disease is more prevalent during the cold seasons.

SIGNORELLI, New Orleans.

EPILEPSY IN INFANCY. A. POUCHE, Pediatria **42**:147 (Feb. 1) 1934.

This article consists in a report of studies on sixty-one epileptic children and a critical review of the literature, with a discussion of the principal problems of this disease in infancy. After explaining the conception of symptomatic epilepsy, the importance of several causal factors and the modality of the onset of this disease in infancy, the author discusses in detail the relation between epilepsy and infantile convulsions.

The principal epileptic manifestations and the special character which these assume in childhood are fully discussed.

SIGNORELLI, New Orleans.

A CASE OF TRANSITORY CERVICOPLEGIA. EDUARDO IMBASSAHY, Arch. de pediat., Rio de Janeiro **6**:449 (Nov.) 1933.

The author reports a case of transitory paralysis in a malnourished infant of considerable hypotonicity, which disappeared spontaneously within four days. Bacteriologically, the nasopharynx showed Bacillus diphtheriae. This however was not a case of diphtheritic paralysis, but a transitory paralysis of unknown origin and rapid evolution. It falls into the category of such cases of transitory paralysis of the neck as those reported by Figueira in 1915. There is a hypothesis that it is similar to acrodynia.

SANFORD, Chicago.

THE SYNDROME OF CONVULSIONS IN INFANCY. NAVANTINO ALVES, Mov. pediat. Belo Horizonte, Brasil **1**:2 (Nov.) 1933.

Alves believes that certain persons have a particular nervous constitution that makes them liable to convulsions. He discusses the various acute and chronic conditions that cause this condition, such as cerebral pathologic change and infectious disease.

SANFORD, Chicago.

IDIOCY WITH ALIMENTARY ANEMIA AND DISTURBED GROWTH. ERWIN THOMAS, Monatschr. f. Kinderh. **59**:105, 1933.

This is a report of two cases of idiocy with anemia of the chlorotic type, marked disturbance of growth and hypotonia. Rachitic changes were also noticed. Thomas believes that the anemia, disturbed growth and rachitic changes were somewhat independent of the idiocy, being due to prematurity as well as insufficient diet.

GERSTLEY, Chicago.

NURSLING'S TETANY. JOSEPH CSAPO, Monatschr. f. Kinderh. **59**:170, 1934.

In a study of tetany in nine nurslings, the writer came to the conclusion that the hypothesis of alkalosis is unjustified and that the metabolism does not even necessarily lean to the alkaline side. Tetany can occur with an outspoken tendency toward acidosis. The real cause of tetany is a diminution in calcium. Phosphorus also plays a rôle, as does the amount of water in the tissues. Bicarbonates are affected not so much by the intensity of breathing as by the state of the fixed bases, chlorides, organic acids, phosphates and protein. Definite loss of water may cause disappearance of the symptoms, which recur when water is again retained.

GERSTLEY, Chicago.

PROGRESSIVE MUSCULAR ATROPHY TREATED WITH ROENTGEN RAYS. P. VON KISS and P. VON MESCOLY, Monatschr. f. Kinderh. **59**:183, 1934.

The case of a 13 year old girl who had been ill for one year is reported. Five treatments consisting of the application of roentgen rays to the spine were given. After the second treatment improvement began, and six weeks after the fourth treatment some muscular function returned. Within another six weeks the reflexes were manifest.

GERSTLEY, Chicago.

TECHNIC OF CISTERNAL PUNCTURE. ARTHUR VON SARBÓ, Wien. klin. Wchnschr. **46**:996 (Aug. 11) 1933.

Von Sarbó, after describing this procedure, states that he has been able to simplify the operation greatly and that he has not failed in any case in the application of the method, nor have any of the usual unpleasant incidents been present. The object of this article is to urge physicians to use this procedure more frequently than in the past. The author stresses the fact that cisternal puncture cannot replace spinal puncture, and that if it is desired to obtain fluid, lumbar puncture should be done, since there are cases in which only the spinal fluid is changed. Cisternal puncture is chiefly used in cases in which repeated examination of the fluid (as in syphilis) or therapeutic withdrawal of fluid (as in epilepsy and meningitis) is necessary. The great advantage of cisternal puncture, aside from the fact that it is almost painless, is that the patient need not go to bed after the procedure, as in lumbar puncture, but may return to his regular activities after remaining seated for from one to two hours.

ABT, Chicago.

PROGNOSIS IN PURULENT MENINGITIS. ERNST A. PRIBRAM, Wien. klin. Wchnschr. **46**:1001 (Aug. 11) 1933.

Pribram cites the work of Edelmann, which demonstrated a valuable addition in the diagnosis of spinal fluid, and also cites two personal observations.

A favorable prognosis in regard to meningococcic therapy in the presence of not too numerous gram-negative, intracellular diplococci (meningococci) applies only to patients older than 5 years. The prognosis is unfavorable for younger children. In spite of the greatest care in treatment, it has been impossible to save any of the younger patients because of the fact that only the first lumbar puncture and injection of serum has been successful. The narrow spinal space soon becomes clogged with pus, and even the most experienced physician has not succeeded in

withdrawing a drop of fluid. Injection of serum is not possible. A study of this purely technical question, which is of vital importance to the patient, is desirable

The second observation concerns the presence of leukocytes without micro-organisms. The prognosis is favorable if this occurs in meningococcic meningitis. A culture will show meningococci, if it is obtained prior to the injection of serum. There are, however, cases of streptococcic meningitis (mostly otogenous) without the presence of micro-organisms in the pus of the spinal fluid. Since meningococcic serum is not effective in these cases and since cultures are slow in growing, the history, which almost invariably points to preceding otitis media, must be considered in making the diagnosis. The patient may probably be saved by intraspinal injection of antistreptococcic serum or, better, of convalescent serum from a patient recovering from otitis media. Without positive findings it is difficult to convince the physician of the necessity of such therapy, and after the culture proves to be positive (in about two days) it is too late for action, and the patient fails rapidly. For this reason the prognosis is unfavorable. Only the most carefully taken history may point to the life-saving therapy.

ABT, Chicago.

DIAGNOSIS OF TUMOR OF THE BRAIN IN EARLY CHILDHOOD. E. STRANSKY, Acta pædiat. **15**:12 (Nov. 6) 1933.

Tumors of the brain are relatively uncommon in infancy; the diagnosis is rendered difficult by the frequent absence of both general and focal symptoms. Beyond the age of infancy their frequency increases rapidly. In an analysis of 1,028 intracranial neoplasms in patients of all ages, Critchley found 125 (12 per cent) in persons under 16 years of age. Of these, 27 per cent involved the medulla and cerebellum, 19 per cent the cerebral hemispheres and 11 per cent the hypophyseal region. Etiologically, tuberculoma was the most common tumor; this was followed by glioma, sarcoma and, with greater rarity, gumma, endothelioma and neurofibroma. The symptomatology is extremely uncharacteristic. In addition to the more generally recognized manifestations, it includes dwarfism and epileptic attacks, as well as meningeal and encephalitic syndromes. Although encephalography may confirm the presence of tumor, exact localizing diagnosis is frequently difficult. The presence of calcification may be helpful from a roentgenographic standpoint. Indispensable information is occasionally obtained from examination of the spinal fluid, which may show an increased protein content, xanthochromia or erythrocytes and tumor cells.

The author reports two cases of tumor of the brain in infants. The first patient was a boy, aged 4 months. The presence of tumor was suspected because of rapid enlargement of the head. Papilledema, optic atrophy and convulsions were absent. The diagnosis was confirmed by observing tumor cells (endothelial) in the ventricular fluid and by roentgenographic demonstration of a shadow of the density of calcium at the base of the brain. The infant was treated intensively with the roentgen rays. At the age of 18 months the process seemed stationary, although the shadow had persisted and had increased in size. In the meantime, excessive adiposity had developed but there were no symptoms of diabetes due to disturbance of the pituitary gland.

The second patient was a boy who, at the age of 18 months, commenced to show rapidly progressive hydrocephalus together with convulsions. The spinal fluid protein was increased to 250 mg. per hundred cubic centimeters. Death followed surgical exploration. Autopsy disclosed a widespread dural endothelioma, originating at the base of the brain.

The case of a third patient is described to illustrate the sometimes insuperable nature of the obstacles encountered in the differential diagnosis of intracranial disease in infancy. The patient was a 16 month old infant who presented many of the classic features of tumor of the brain. Autopsy revealed sepsis, diffuse cerebral thrombosis with secondary encephalomalacia and a congenital anomaly in the decussation of the pyramidal tracts.

MCCUNE, New York.

RÔLE OF MIXED INFECTION IN THE ETIOLOGY OF PURULENT MENINGITIS IN INFANCY. M. M. ZIMBAL and P. A. ALISSOF, Acta pædiat. **15**:68 (Nov. 6) 1933.

This report comes from Leningrad, where an increase in the incidence of cerebrospinal meningitis occurred during 1931 and continued through the first six months of 1932. Of one hundred and seventy-three patients with purulent meningitis seen by the authors during this period, almost 20 per cent showed either the simultaneous or the serial presence of two or occasionally three infecting organisms. All the patients with mixed infection were in the first two years of life. In most secondary invaders were: Pneumococcus, Diplostreptococcus, Friedländer's bacillus cases the meningococcus was the primary organism; in order of frequency the and Pfeiffer's bacillus. The highest incidence of mixed infection was found in infants between 3 and 9 months old; the disease was commonest during February. Secondary invasion of the meninges was frequently related to the antecedent onset of pulmonary or otic complications of the original illness. In several cases postmortem bacteriologic studies demonstrated the identity between the organisms found in the ears or lungs and those previously found in the cerebrospinal fluid. Carefully controlled asepsis in the performance of lumbar puncture excluded the possibility of accidental surgical infection of the meninges.

The general mortality for uncomplicated meningococcic meningitis in 1931 was 44 per cent; the mortality for patients with mixed meningococcic infections was 67 per cent (Meningococcus and Pneumococcus, 81 per cent; Meningococcus and Friedländer's bacillus, 66 per cent; Meningococcus and Diplostreptococcus, 50 per cent). The younger the patient the higher was the mortality. Twenty-one cases of mixed infection were treated with antimeningococcic serum; the results seemed beneficial. Intramuscular injection of a parent's blood was thought to be valuable. The occurrence of hydrocephalus was somewhat more common after a mixed infection.

The authors discuss the pathogenesis of secondary invasion of the meninges. No blood cultures were taken from the patients in this series.

McCUNE, New York.

CONGENITAL PSEUDOBULBARPARALYSIS AND SYMPTOMS OF THE EYE. A. J. AALBERS and R. VEDDER, Maandschr. v. kindergeneesk. **2**:570 (Sept.) 1933.

This article contains the description of a typical case of the paralytic form of this rare condition in a girl, aged 11 years.

VAN CREVELD, Amsterdam, The Netherlands.

Diseases of the Eye

MICROPHTHALMOS WITH CONGENITAL DEFECT OF THE LACRIMAL APPARATUS. S. SILVERMAN, Brit. J. Ophth. **17**:351 (June) 1933.

The specimen was taken from a female twin who died at about the age of 3 months.

The right eye presented a coloboma of the iris at its lower pole.

On the left side there was a cystic structure in the position of the lacrimal sac. A punctum was present in the normal position in the lower lid, but no communication with the cyst could be established, nor could any communication with the nose via a nasal duct be made out. The cyst was tense and contained a colorless serous fluid. The walls were of tough fibrocellular structure. The eyeball was smaller than that of the right side. There was a coloboma of the iris at the lower pole.

The origin of the cyst is discussed and the conclusion expressed that it was apparently an instance of overgrowth and distention of the lacrimal sac, with arrested development of the left eyeball and incomplete canalization of the inferior canaliculus and of the nasal duct, combined with some slight failure in the normal involution of both choroid fissures.

ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

PERSISTENCE OF THE CIRCULATION IN THE POSTERIOR VASCULAR SHEATH OF THE LENS IN THE RIGHT EYE OF A GIRL AGED FOURTEEN YEARS. H. TOMKIN, Brit. J. Ophth. **18**:39 (Jan.) 1934.

In the case which Tomkin reports a fine strand of pupillary membrane extended obliquely from the iris onto the anterior capsule of the lens. There were a few punctate opacities in the anterior cortex of the lens. Immediately behind the lens was an opacity in which vessels were radiating. It was thickest centrally, gradually thinning to the periphery, and occupied the middle third of the posterior part of the lens. The opacity was thin and irregular and had a serrated margin. Through the center a small opening could be seen—the point of entrance of the hyaloid artery, which divided into a descending branch and two nasal branches, the latter uniting again into a common trunk. With the slit lamp blood was seen coursing away from the center in all the branches. The lower column could be traced as far as the posterior surface of the iris. The common trunk could be traced a short distance and disappeared behind the iris. A number of fine gray strands were also seen, which had the appearance of obliterated vessels of the hyaloid artery. When the main trunk of the artery was traced backward with the ophthalmoscope, it appeared black, but a red glint along the upper border could be detected. The column was traced back to the disk. The hyaloid artery came from the central artery and was involved in connective tissue for part of its course from the disk. Color plates accompany the article. [A similar case has been reported by C. A. Young, of Roanoke, Va. W. Z.]

ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

STRABISMUS AND AVITAMINOSIS. L. DOR, Arch. d'opht. **50**:667 (Oct.) 1933.

The question of the etiology of strabismus still remains confused. Dor briefly states the various suggestions as to its cause. Believing that it may be due to arrested development imputable to faulty nutrition, he has treated many strabismic patients with vitamins without greater success than attends the usual methods. Mouriquand showed that vitamin therapy is effective only in recent avitaminosis and is inactive in long-standing conditions. Dor waited for a recent case of strabismus in a child to try this form of treatment. Such a case he describes in detail. The child was first seen when 11 months old. Its mother had been operated on for convergent strabismus, and other relatives on the maternal side were similarly affected. With the administration of a mixture of vitamins A and D Dor noted the disappearance of the strabismus. When the administration of these vitamins was stopped the strabismus recurred, and disappeared on readministration. Dor discusses the objections which may be raised in this case. He cites another instance in which the mother of a strabismic child had had an enteritis during pregnancy and a diet lacking in vitamins. During a second pregnancy the same diet was used with the addition of vitamins. Strabismus did not occur in the second child. As a result of these observations Dor suggests that while the vitamins may be sufficient for the normal development of the eyes of a normal child, they may be insufficient for the proper development of those of a child with a hereditary predisposition to strabismus.

MARLOW, Syracuse, N. Y. [ARCH. OPHTH.]

THREE CASES OF COLOBOMA OF THE OCULAR MEMBRANES. E. LAZARESCU and D. LAZARESCU, Arch. d'opht. **50**:760 (Nov.) 1933.

The authors discuss the three theories which have been proposed to explain coloboma. The ectodermic theory of von Szily best explains incomplete closure of the fetal fissure. Deutschman's theory of inflammation best explains the atypical forms of coloboma. The first case presented is one of bilateral coloboma of the iris and choroid. The choroidal coloboma in the right eye included the optic nerve entrance. There was also a slight degree of microcornea. The second case is that of an atypical partial coloboma of the optic nerve involving the macula.

The third case is one of an isolated coloboma situated in the superior temporal region of the left eye and having the appearance of a second, atrophic disk.

MARLOW, Syracuse, N. Y. [ARCH. OPHTH.]

TREATMENT OF FAMILIAL DEGENERATION OF THE CORNEA: REPORT OF TWO CASES OF THE GROENOUW TYPE. LOTTE HAGER, Klin. Monatsbl. f. Augenh. **91**:593 (Nov.) 1933.

Prompted by Löwenstein's favorable report on his therapy for familial degeneration of the cornea (*Klin. Monatsbl. f. Augenh.* **82**:752, 1929), two patients with the Groenouw type were satisfactorily treated in the same manner at the University Eye Clinic in Tübingen. The treatment consists in the production of intense hyperemia by daily massage of the eyes with a salve composed of ethylmorphine hydrochloride and mercury, diathermy and the administration of iodine hypodermically and saline solution subconjunctivally.

The first patient, a woman, aged 35, had at the center of the cornea fine subepithelial nodules and star-shaped changes in the parenchyma. Coarser opacities were observed in the superficial, and finer ones in the deeper, layers. The space between the opacities showed some fine clouding. Vision rose from 5/18 to 5/8 of normal in each eye. The dense opacities remained unchanged, but the veil between them became decidedly clearer.

The second patient, a girl, aged 17, had myopia of 6 diopters in the right eye and of 10 diopters in the left, with vision of 5/18 in each eye. Nodular opacities were noticed in the center of the cornea in both eyes; the periphery was clear. The nodules were slightly opalescent, had irregular borders and were located chiefly in Bowman's membrane, though some were in the deeper layers of the parenchyma; they were distinctly separated, and the interspaces were clear in the right eye, while they were confluent, forming larger figures connected by a diffuse gray veil, in the left.

The nodules were reduced in number, and some were decreased in size; some of those in the left cornea became distinctly separated, and the interspaces grew clearer. Vision was finally 5/5 in the right eye and 5/6 in the left. The result of this therapy depends on the willingness of the patient to remain under treatment sufficiently long, lest recurrences occur, as in the first case. The time was too short to decide whether the results in these cases were permanent.

STOLL, Cincinnati. [ARCH. OPHTH.]

Diseases of the Skin

NEUROFIBROMATOSIS IN A CHILD. L. BABONNEIX and DUCROQUET, Bull. Soc. de pédiat. de Paris **31**:132 (March 21) 1933.

A girl, 11 years old, showed the characteristic manifestations of Recklinghausen's disease. She had numerous hairy and pigmented areas of skin over the body, which tended toward a segmental distribution; some discrete cutaneous tumors, and a number of growths along the course of the right median nerve. Mentally she was distinctly retarded.

BENJAMIN, Montreal, Canada.

ACRODYNIA: IS IT A CONTAGIOUS DISEASE? PRESENTATION OF TWO BROTHERS WITH ACRODYNIA. G. BLECHMANN, H. MONTLAUR and A. LECONTE, Bull. Soc. de pédiat. de Paris **31**:135 (March 21) 1933.

Two brothers, born a year apart, both showed signs of acrodynia. An older brother presented no evidence of the disease. The occurrence of acrodynia in two members of a family was reported by previous observers. The possibility of an infectious etiologic factor is mentioned, although this communication does not furnish adequate evidence to substantiate it.

BENJAMIN, Montreal, Canada.

INTOLERANCE FOR MILK: ECZEMA; EDEMA; VALUE OF HIGH PROTEIN AND HIGH CALORIC DIET. J. CATHALA, P. DUCAS and A. NETTER, Bull. Soc. de pédiat. de Paris **31**:224 (May 16) 1933.

A boy, 7 months old, showed marked eczema and edema. He had been fed many types of diet, but failed to thrive on any of them. It is believed that he had an intolerance for milk. No allergic tests were made. He was fed preparations of vegetable protein, liver and egg, and was given some cod liver oil and orange juice, as well as thyroid extract. He improved on this regimen.

BENJAMIN, Montreal, Canada.

TWO CASES OF SEVERE UNNAMED DERMATITIS. L. DE KEYSER, Rev. belge sc. méd. **5**:682 (Nov.) 1933.

The dermatitis in the cases reported was a fulminating fatal cutaneous condition of which the author finds no record in the literature. The first patient, a girl of 15, presented on admission to the hospital numerous fiery red plaques on the face, which were polycyclic, oily and bounded by an elevated border. Bullae speedily appeared on the limbs and became spreading plaques resembling those on the face. Then a gangrenous appearance developed about the nose and periorbital region, while the general health of the patient declined. Six days after admission she died.

The second patient was 62 years old and suffered from spreading ulcerative moist lesions of the nose and postauricular region. After a few days bullae appeared on the limbs; these had a purulent hemorrhagic appearance. They soon ruptured, and a fungus developed on their bases. In this patient, too, the general health became greatly impaired, and death supervened a month later.

Cultures of the pus showed Staphylococcus albus in the first patient and Staphylococcus albus, streptococci and pseudodiphtheria bacilli in the second. Pathologic examination showed only common granulation tissue. In spite of the unsatisfactory results of his bacteriologic study, de Keyser believes the process to be infectious.

VINTON, Brooklyn.

HERPES ZOSTER AND VARICELLA. K. SCHRAUBE, München. med. Wchnschr. **80**:1438 (Sept. 15) 1933.

Schraube reports the occurrence of herpes zoster and varicella in the same family. Nineteen days after herpes zoster developed in the mother her daughter showed the first symptoms of varicella. Herpes zoster generalisata was ruled out in the daughter by the presence of lesions in the mouth, the duration of the lesions and the absence of sensory disturbances. Schraube concludes that both diseases were caused by the same virus.

BRAHDY, Mount Vernon, N. Y.

Surgery and Orthopedics

EARLY DIAGNOSIS AND TREATMENT OF CONGENITAL DISLOCATION OF THE HIP. J. A. FREIBERG, J. A. M. A. **102**:89 (Jan. 13) 1934.

The early diagnosis of congenital dislocation of the hip is not difficult. Asymmetrical folds of skin in the thigh are valuable in making a diagnosis in unilateral congenital dislocation of the hip, as is the observation of deeper creases on one side of the mesial aspect of the thigh than on the other. In bilateral dislocation asymmetry is not present, but the folds are deeper on both sides. Eversion or external rotation of the affected leg is another early diagnostic sign. Shortening is not always easy to demonstrate. Palpation of the area of the hip joint reveals further abnormality, if the infant is not too obese. Such findings should suggest roentgen examination. Diagnosis before the age of 6 months is helpful, for reduction by gradual abduction of the legs may be accomplished. Several methods of treatment are described.

BONAR, Salt Lake City.

THE SUITABLE TIME FOR SURGERY IN CHILDREN. IRWIN SCHULZ, Wisconsin M. J. **32**:820 (Dec.) 1933.

For several reasons, such as structural delicacy, changing proportions in organs during growth, less percentage of blood, with greater tendency to shock, instability of physiologic processes, with more rapid development of dehydration and acidosis, and other conditions, pediatric surgery presents special problems. More careful selection of the best time for operation is needed to insure better results. Surgical treatment for certain congenital defects and in emergency must or should be carried out at once or early. These conditions include clubfoot, congenital pyloric stenosis, congenital dislocation of the hip, harelip and cleft palate, imperforate anus, congenital intestinal atresia and wryneck. In other conditions of childhood surgical treatment is much safer and gives better results if deferred till the patient is 2 years of age or older, as indicated. Such conditions are undescended testicles, webbed fingers, hydrocele, uncomplicated hernia, both inguinal and umbilical, and exstrophy of the bladder.

JANNEY, Wauwatosa, Wis.

ON LATERAL TILTS OF THE PELVIS IN CHILDREN. EDGAR CYRIAX, Brit. J. Child. Dis. **30**:274 (Oct.-Dec.) 1933.

Lateral pelvic tilts due to primary malrotation of the fifth lumbar vertebra on the sacrum are the prime consideration in this article.

It has been definitely demonstrated that normally each lumbar vertebra can be rotated through about 2 degrees, there being a range of 3 degrees in the lumbosacral joint. Greater degrees of pathologic rotation can occur in the lumbar vertebrae. This is because the latter movement, instead of taking place round a center situated in the anteroposterior midline of its body, does so around a center situated in the articular processes and continues through the body and spinous process of the bone, moving in opposite directions, until arrested by ligamentous or muscular tension.

These malrotations are much commoner in girls, because of the greater laxness of the lumbosacral joint. The immediate cause is nearly always a sudden twisting of the trunk. Actual trauma is also sometimes a cause. The actual displacement per se in most instances produces no symptoms. It may be weeks or even months before backache manifests itself in this area and medical advice is sought.

When the child takes the "stand at attention" position the lateral pelvic tilt is corrected, but temporary scoliosis in the lumbar vertebrae is brought out. Another sign is that the umbilicus no longer lies equidistant from the two anterior superior spines, respectively.

Replacement of the displaced bone should be attempted in every case unless contraindications exist. Cyriax describes his method.

LANGMANN, New York.

EMPYEMA IN CHILDREN FROM THE PHYSICIAN'S POINT OF VIEW. HUGH T. ASHBY, Brit. J. Child. Dis. **31**:1 (Jan.-March) 1934.

Taking pneumonia as a whole, about from 10 to 12 per cent of the cases are complicated by empyema. At the outset it is most important to distinguish between the two distinct types of empyema: (1) synpneumonic and (2) metapneumonic.

Synpneumonic empyema is best dealt with by repeated aspiration until the child can stand open resection of the ribs—usually within a week or ten days. In metapneumonic empyema it is best to operate as soon as possible. Ashby advocated resection of ribs. Continuous suction drainage is often unsatisfactory.

In infants empyema is always serious, and repeated aspiration has proved the most satisfactory form of treatment. In cases that are of pneumococcic origin the author advocates injecting optochin into the pleural cavity after the pus has been drawn off. The process may be repeated two or three times, if necessary.

LANGMANN, New York.

THE MECHANICS OF APPENDICITIS. B. W. WILLIAMS and R. H. BOGGON, Lancet **1**:9 (Jan. 6) 1934.

In the great majority of cases of acute appendicitis (97.2 per cent) the condition results from acute obstruction of the lumen of the appendix. This obstruction is produced by a preexisting fibrotic stricture of inflammatory origin in the submucosa. In recurrent appendicitis a fibrous stricture is present in the submucosa, as in acute appendicitis. Chronic inflammatory appendicitis in the absence of fibrous stricture has not been observed.

LANGMANN, New York.

TREATMENT OF PNEUMOCOCCIC EMPYEMA IN INFANCY WITH SODIUM TAUROCHOLATE. G. CAREDDU, Arch. ital. di pediat. e puericolt. **2**:167 (Jan.) 1934.

Careddu treated thirty-three children (ranging in age from 9 months to 11 years) for pneumococcic empyema by means of intrapleural injections of sodium taurocholate (from 2 to 20 Gm.). All but three recovered.

DOOLEY, New York.

EARLY OPERATION IN PNEUMOCOCCIC PERITONITIS. WERNER BUDDE, Arch. f. klin. Chir. **178**:308 (Dec.) 1933.

Budde discusses the differential diagnosis of this condition, presenting cases in illustration. Pneumococcic peritonitis is merely the most evident symptom in a severe generalized pneumococcic infection. Treatment therefore should be directed to the whole infection, preferably with serum or optochin-base. Early operation, which most surgeons have abandoned in this condition, seems to do damage in increasing shock and in altering too abruptly intra-abdominal pressure.

DAFFINEE, Boston.

OPERATION FOR CONGENITAL HARELIP AND CLEFT PALATE. H. PICHLER, Wien. klin. Wchnschr **47**:70 (Jan. 19) 1934.

Pichler notes that in 1931 a book by Veau appeared in Paris concerning cleft palate. A second book by one of his students, Plessier, treated of harelip. Veau's methods appear to the author to be such a distinct advance that he discusses them in detail. He used these methods in forty-three cases of congenital harelip and cleft palate. The success obtained was so much greater than by other methods that it can hardly be looked on as a coincidence. For example, among sixty-six patients with cleft palate who were operated on according to Langenbeck's method and similar methods, 32.9 per cent were cured after the first operation, and 52.3 per cent were partially cured. Among forty-three patients who were operated on by Veau's method 74.4 per cent were cured after the first operation, and 20.9 per cent were partially cured. Pichler states further that since he became acquainted with Veau's method, he regards all other methods as of historical interest only.

ARTHUR F. ABT, Chicago.

Miscellaneous

NORMAL SLEEP PATTERN FOR CHILDREN. G. GIDDINGS, J. A. M. A. **102**:525 (Feb. 17) 1934.

The child has a definite sleep pattern that is rarely disturbed except through sickness or certain experimental conditions. Sleep is definitely quieter in cold weather than hot. Six ounces (177.4 cc.) of warm milk at bedtime seems to produce quiet sleep in normal children, but of the other beverages tested, such as orangeade or caffeine-containing cold beverages, none seem to affect sleep. A large amount of plain food results in restlessness, which persists in many cases throughout the night. Warm or cold baths on retiring have no constant effect in either producing or interfering with sleep.

BONAR, Salt Lake City.

THE ABSORPTION OF METHYL SALICYLATE BY THE HUMAN SKIN. ERNEST W. BROWN and W. O. SCOTT, J. Pharmacol. & Exper. Therap. **50**:32 (Jan.) 1934.

The cutaneous absorption (in adult males) of methyl salicylate, both undiluted and in various solutions, was investigated, and the amount absorbed was determined on the basis of urinary excretion. The greatest absorption resulted from immersion of the hands in an 11.8 per cent solution by volume of the ester; then from immersion in a 50 per cent solution in alcohol and least from immersion in the pure ester (less than one sixth of the aqueous solution). In oily vehicles (50 per cent solution) there was an increase in the amount of substance absorbed over the amount of pure ester absorbed as follows: oil and lard oil, 29 per cent; liquid petrolatum, 65 per cent, and hydrous wool fat, 117 per cent. Massage increased the absorption of the pure ester as much as 158 per cent; increase of the temperature of the bath from 26 to 43 C. also greatly increased absorption.

PILCHER, Cleveland.

THE EFFECT OF PATHOLOGIC STATES ON THE MINIMUM LETHAL DOSE OF PROCAINE INTRACISTERNALLY. FRANK WANG COTUI, J. Pharmacol. & Exper. Therap. **50**:51 (Jan.) 1934.

Cotui found that pneumonia, postoperative infections, and low blood pressure resulting from hemorrhage, nitrite and histamine all made possible a reduction in the intracisternal dose of procaine hydrochloride necessary to paralyze the respiratory center of dogs. Each of these states is associated with anoxemia. In previous work a number of narcotics used for preanesthetic medication had no such effect, but sodium amytal did.

PILCHER, Cleveland.

THE COMPARATIVE EFFECT OF VARIOUS DIURETICS IN DOGS WITH SPECIAL REFERENCE TO THE EXCRETION OF URINE, CHLORIDE, AND UREA. MARSHALL N. FULTON, HOWARD A. VAN AUKEN, ROBERT J. PARSONS and LOWREY F. DAVENPORT, J. Pharmacol. & Exper. Therap. **50**:223 (Feb.) 1934.

Of the diuretics studied the greatest urinary volume of output followed the use of mersalyl, with and without ammonium chloride, and merbaphen; other diuretics caused a much lower output. These drugs and several others also caused a great increase in urinary chloride, even when there was no increased blood chloride, and with such increase in the excretion of chloride blood chloride was lowered. The results are discussed in relation to theories of the action of diuretics.

PILCHER, Cleveland.

DIRECTORSHIP OF THE SCHOOL HEALTH PROGRAM. FREDERICK L. PATRY, New York State J. Med. **34**:105 (Feb. 1) 1934.

Among the necessary qualifications for the directorship of school health education and school health service a medical degree is the primary requisite. One year of pedagogic training, as well as the bachelor's degree in arts or science, is also essential. Administrative ability is very essential.

AIKMAN, Rochester, N. Y.

CHILD WELFARE MOVEMENT IN THE UNITED STATES. J. H. MASON KNOX JR., Rev. franç. de puéricult. **2**:48 (Feb.) 1934.

Child welfare work in the United States is performed by numerous agencies: the United States Public Health Service, the federal Children's Bureau, the state bureaus of child hygiene and analogous institutions in all the large cities. Several important private foundations contribute largely to the work. Prenatal care is easily available for children of the upper economic strata and for the poor in cities. It is children of the lower middle class and those in rural districts who receive inadequate prenatal care. In certain states much is being done to improve

this situation. The reduction of infant mortality is a satisfactory result of the measures taken for child hygiene in the United States. This result is due to numerous factors, in particular, the qualitative improvement in the milk, the extension of the supervision of infants by doctors and nurses and the greater interest which parents take in these questions.

CRANE, Chicago.

OIL OF CHENOPODIUM IN PHARMACOLOGY, MEDICINE AND TOXICOLOGY. A. MANCINI, Riv. di clin. pediat. **31**:1281 (Nov.) 1933.

In a critical review Mancini draws the following conclusions regarding oil of chenopodium:

1. It is undoubtedly the most efficacious anthelmintic known for hookworm and round-worms. 2. It is a mixture of substances of various composition; some of its constituents are without anthelmintic action, but one of them ascaridol is very efficacious. 3. The composition of oil of chenopodium is inconstant, varying with the individual plants and the technic of preparation. 4. There is no chemical method of standardization, but a method of biologic standardization has been suggested. 5. The margin between the therapeutic dose and the toxic dose is so small as to render its clinical use risky, especially in children, who are particularly susceptible to the drug. 6. Since pharmaceutic and pharmacologic research has not been able to offer an oil of chenopodium of constant chemical composition or pharmacologic action, its use should be strictly limited because of the danger of poisoning, in spite of its high therapeutic efficacy.

HIGGINS, Boston.

PHYSICAL CULTURE IN INFANCY. C. F. DE ABREU, Arch. de pediat., Rio de Janeiro **6**:481 (Jan.) 1934.

De Abreu shows by photographs various exercises for the infant early in the first year. He believes that physical education is essential in infancy.

SANFORD, Chicago.

NORMAL AND PATHOLOGIC LEAD CONTENT OF THE TEETH OF MAN AND ANIMALS. F. PFRIEME, Arch. f. Hyg. **111**:232 (Jan.) 1934.

Lead is present in the teeth of all normal persons. The average lead content of the teeth of fifty-seven normal persons was 0.135 mg. per hundred cubic centimeters. In three cases of lead poisoning the average was 0.42 mg. The lead content of the teeth is negligible in the very young and increases progressively with age. There is no lead in the tartar of teeth; traces are present in the enamel, but most of the lead is present in the dentin. Sex and place of dwelling are not factors. The teeth of carnivorous animals contain the most lead, those of omnivorous the second largest amount and those of herbivorous animals the least.

GLASER, Rochester, N. Y.

ZINC POISONING IN A THREE YEAR OLD CHILD. H. TUNGER, Monatschr. f. Kinderh. **59**:265, 1934.

A 3 year old child drank a 50 per cent solution of zinc chloride containing 6 Gm. of the salt. The symptoms were those of corrosive poisoning, with collapse, dyspnea and soft pulse. The knee jerk reflexes were not elicited. Vomiting and diarrhea were marked, with blood. The child improved for a few days, then showed signs of peritonitis and died following operative opening of the abdomen. Postmortem examination showed that peritonitis had resulted from corrosive perforation of the stomach.

GERSTLEY, Chicago.

ACTIVITIES OF PHYSICIANS IN ELEMENTARY SCHOOLS IN LODZ IN 1931 TO 1932. STANISLAUS GUTENTAG, Zycie Dziecka **3**:1 (Jan.) 1934.

The rôle of school physician is very important. He cannot limit himself to medicine; his work should include the care of the child's health, attention to the

child's physical and mental development, the prevention of all mishaps in school life and contact with the child's home life. He does not treat the child, but practices preventive medicine in all its branches. This work requires cooperation with the personnel of the school. The system used in the elementary schools in Lodz is extensive and detailed. Each child is given a thorough physical examination, the results of which are recorded on a health card. Besides a dental department, there are a nutritional department and, what is most important, a special department for children with congenital syphilis.

KRUPINSKI, Chicago.

DYNAMICS OF THE PHYSICAL DEVELOPMENT OF ADOLESCENCE. T. T. BRASLAVSKI, Okhr. Zdor. Det. i Podr., no. 5-6, 1933, p. 49.

Studies made in 1925, 1929, 1930 and 1931 on adolescent children were reviewed, the standards of physical development were taken from (1) the height, weight and circumference of the chest; (2) the size and coefficient of variation; (3) the height-weight index and the index of height and circumference of the chest. These studies showed an improvement in the physical condition of the children since 1925. This was especially emphasized in the coefficient of variation. The diminution in the size of subjects 17 years of age at the time of writing is attributed by Braslavski to the fact that these would probably have died under their previous condition as laborer's children.

SEMENENKO-MCKHANN, Boston.

Society Transactions

PHILADELPHIA PEDIATRIC SOCIETY

Oct. 9, 1934

JOHN D. DONNELLY, M.D., *Chairman*

JAMES E. BOWMAN, M.D., *Secretary*

FUNCTIONAL AND DEVELOPMENTAL SPACE RETAINERS FOR LOSS OF DECIDUOUS TEETH. DR. RICHARD C. MEARS.

The functions of the deciduous teeth are: (*a*) to act as organs of mastication, (*b*) to aid in the development of the mandible and maxillae, (*c*) to guide the permanent teeth into the correct position, (*d*) to maintain a correct relationship between the mandible and maxillae until the permanent teeth erupt, (*e*) to aid in the muscular development of the face and (*f*) to aid in enunciation.

For these reasons the deciduous teeth should be preserved until exfoliation. Children should be taken to the dentist when the first dentition is complete and periodically thereafter.

Cavities in deciduous teeth should be filled if there is no pulpal involvement. Teeth with exposed pulp chambers should be extracted whether they are causing the patient discomfort or not, as they are a source of focal infection. Children with infected teeth have a lowered resistance, are irritable and cannot masticate their food properly.

Impairment of the function and development of lost teeth is corrected by artificial replacements in the form of bridges or plates. These appliances are the best known substitutes for natural teeth and prevent later disorders, namely, those resulting from improper mastication of food, lack of bone and muscular development of the face and orthodontic appliances.

DISCUSSION

DR. PHILIP S. BARBA: Dr. Mears has done very interesting work with these appliances. I saw one boy who lost weight for a couple of years, with practically no mastication at all, who ate strained vegetables and ground beef. After Dr. Mears put in plates and dentures the boy became very different and gained weight. Several other patients have shown definite improvement, not so much in weight as in a substantial increase in tissue tone and the general condition. The surprising thing is the way that the appliances work. I was a little skeptical at first about the child's ability to keep them in place and in the ability to handle these children. It seems to have worked out very well. There is practically no trouble in getting the children to take care of the appliances themselves. They are interesting to me as a practical preventive because I have had great expense getting my own children's teeth straightened. I think something of this kind should be encouraging in keeping the child's mouth clean. We have all seen cases of abscessed teeth and draining fistulas with toxic symptoms as a result of abscessed teeth. Anything that will encourage the removal of the diseased teeth, shape the jaw and space the second teeth is a great help in the development of the child's nutrition. Dr. Mears is to be congratulated on developing the work.

SYMMETRICAL SEROUS SYNOVITIS (CLUTTON'S JOINTS). DR. JOSEPH V. KLAUDER and DR. HAROLD F. ROBERTSON.

Clutton, in 1886, described painless bilateral hydrarthrosis of the knee joints unassociated with the bony changes occurring in congenital syphilis.

Although this type of synovitis is a frequent symptom of congenital syphilis, it has not received the attention it deserves. Little or no mention of this condition has been made by American authors. It is variously termed symmetrical synovitis, symmetrical serous synovitis, hydrarthrosis, hydrops, painless effusion of the knee joints and Clutton's joints.

The majority of the patients are between the ages of 8 and 15 years. In our series of 63 patients the youngest patient was 5 years, and the oldest was 35. Among our total number of 363 patients with congenital syphilis Clutton's joints were present in 17.3 per cent. A slightly greater incidence was demonstrated in patients with interstitial keratitis than in other patients with congenital syphilis. There is a striking similarity between symmetrical synovitis and interstitial keratitis. Both conditions are characteristic of congenital syphilis, occur most frequently in the same age group and affect females more frequently than males.

In conclusion, it may be said that Clutton's joints are a valuable sign of congenital syphilis. Examination of the joints, especially the knees, should not be neglected in the search for evidence of congenital syphilis. Painless effusion of the knees is of prognostic significance. Every child with congenital syphilis is a potential subject for interstitial keratitis, especially in the age group already mentioned. It appears that the presence of Clutton's joints increases the likelihood of interstitial keratitis.

DISCUSSION

DR. HAROLD F. ROBERTSON: I should like to read a short paragraph from Clutton's original description, which appeared in the London *Lancet* of 1886:

"To recapitulate in a few words the principal features of the condition which was demonstrated by these few cases, one would say that the synovitis was symmetrical, affecting only the knees, that it was of a chronic and painless character, and that all the patients were the subjects of hereditary syphilis. I can offer no satisfactory explanation of the facts here recorded, but must content myself with drawing attention to a few clinical symptoms. At the same time I would like to point out that if the condition which is now under consideration be really due to hereditary syphilis, the similarity between interstitial keratitis and this symmetrical synovitis is so marked as scarcely to require any lengthened explanation. Both knees, like the eyes, are, in my experience, sooner or later affected, and often with an interval between the commencement of the symptoms in each joint. Both diseases are exceedingly chronic, and produce little or no destructive changes in the tissues involved, neither suppuration nor adhesions having occurred in any of the cases that came under my observation. They are also both liable to relapses, and not very amenable to treatment. The age of the patient is another and striking point of similarity, for seven out of the eleven were between eight and twelve years of age. In two cases the symptoms arose at a much later date, but this also occurs in interstitial keratitis, so that even in its rarer forms it corresponds with that disease in this particular—that of the age of the patient. I am at a loss to explain why the knees should be affected in preference to other joints. It is probable that, with further observation, the knees will not be found to occupy this solitary distinction, and that other joints will be seen to be affected in a similar manner. But up to the present time I have not seen this chronic symmetrical synovitis which appears to be associated with hereditary syphilis, in any other joints besides the knees. That it should be symmetrical is only what one expects from our knowledge of the similar manifestations of the disease at this period of life."

DR. HENRY H. PERLMAN: Our experience at the Children's Hospital of Philadelphia has not been as wide as Dr. Klauder's. In more than 200 cases of congenital syphilis only 4 instances of Clutton's joints were found. Much to our surprise, 3 of the patients have been treated with acetarsone recently and have improved remarkably.

DR. JOSEPH V. KLAUDER: The eponym is not familiar to American authors. The term Clutton's joints, I believe, is preferable to the other terms, since it indicates a definite form of serous synovitis.

There is a peculiar susceptibility of the osseous system and of the cornea to disease in congenital syphilis. Interstitial keratitis and involvement of the bones and joints are the most outstanding manifestations of active syphilis in infants and children. The involvement is unilateral at first in each condition, and an interval elapses before the beginning of symptoms on the other side. One eye or one joint is involved to a greater extent than its mate. Both processes pursue a chronic course and produce little or no destructive changes in the tissues. Both conditions respond very slowly to antisyphilitic therapy.

The question was asked whether Clutton's joints resemble Charcot's joints. They do not. Enlargement of Clutton's joints, unlike that of Charcot's joints, is attributed to distention of the joint with fluid; again, there are no bony changes in Clutton's joints, which are present in Charcot's joints. Moreover, Charcot's joints are most commonly seen in men with tabes.

SPONTANEOUS HYPOGLYCEMIA DUE TO HYPERINSULINISM IN A CHILD. DR. ARTHUR M. DANNENBERG, DR. M. A. BELL and DR. BENJAMIN GOULEY.

A physically underdeveloped child had been subject since the age of 13 months to attacks in which he suddenly became weak, pale and then comatose, with crossed eyes, general muscular rigidity, catalepsy and an occasional convulsion. He rapidly recovered from these attacks following the administration of sugar by mouth or parenterally. Laboratory studies revealed the attacks to be due to a low blood sugar level. The sugar tolerance was increased, and there seemed to be failure of normal balance between the factors that control the blood sugar level. The evidence pointed to a state of hyperinsulinism, the cause of which was not determined during the patient's life. He died at the age of 3 years of what appeared to be hypoglycemic shock. Autopsy showed cellular hyperplasia of the individual islands of Langerhans.

DISCUSSION

DR. JOHN P. SCOTT: These cases are very interesting. In a case of von Gierke's disease the liver was tremendously enlarged and was the site of fatty infiltration and degeneration. I am much interested in this disease. We have had a number of children with this condition at the Children's Hospital of Philadelphia. I was particularly interested in two; one was brought in unconscious and would wake up as soon as an intravenous injection of dextrose was given. Later his tonsils were removed, and following tonsillectomy the attacks were less frequent. As to the treatment of these patients with insulin, I do not see how one could expect to get results with such marked changes in the pancreas. An interesting method of attack was outlined by Harris, who advised putting the patient on a low carbohydrate diet. I believe that his claim was that a high carbohydrate diet called forth the endogenous insulin of the pancreas and the response of the pancreas was so great that it oversecreted and caused hypoglycemia. For that reason he advised diets rather low in carbohydrate and high in fat. Another investigator a year or so ago determined sugar tolerance curves for patients on different types of diet and found a rather similar effect: A high carbohydrate diet resulted in a sudden rise and fall of the curve. With a lower carbohydrate diet there were a more gradual rise and fall. That may have some bearing on the condition in the case reported. I do not see how one could expect insulin to work when there were so many changes in the pancreas.

DR. FRANK B. LYNCH JR.: One interesting thing about this case impresses one who has tried to find anything wrong with the pancreas in diabetes. There is definite disease of the pancreas in the case reported. It is disappointing to try to find any pancreatic disease in diabetes. In most cases it is difficult to find any histologic evidence. In other cases there is definite disease of the pancreas, with the islands of Langerhans almost obliterated, but with no apparent effect on the patient's sugar metabolism. I incline to a different point of view as regards the type of disease in the islands in this case. It is hard to determine

where the islands of Langerhans are. I believe that the condition is an embryonic type of underdevelopment of the islands rather than hyperplasia.

DR. BENJAMIN GOULEY: As Dr. Dannenberg said, the histologic sections show the types of pathologic changes other than the changes in the islands themselves. One change is periductal fibrosis. These islands are not normal, and the point that Dr. Lynch has made is well taken, for embryonic islands have much the same appearance, but these islands are much larger than normal or embryonic islands. Second, under high power magnification granularity of the cells of the islands can be seen in the cytoplasm—something which one does not see in embryonic cells. Third, there has been chronic pancreatic disease of periductal type with partial occlusion of the large ducts (the attacks of vomiting may have had some relationship to it). There is a physiologic response to ductal occlusion, as is well known. If the ducts are partially obstructed, destruction of the acini of the pancreas and stimulation for the time being of island tissue occur. That is part of the secret of the isolation of insulin by Banting. These islands are larger than normal and intensely granular, and I think that what has occurred here has developed since the child was born. Given small islands with the cells clumped together and nongranular, it would be very hard to tell the difference between them and embryonic islands. In view of the reasons set forth, I think that the pathologic changes developed since birth. The point made by Dr. Goldstein about hyperinsulinism depends on one's point of view after looking at the sections. I think that the condition was hyperinsulinism.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

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Ann Arbor, Mich., Nov. 23 and 24, 1934

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EARLY DIAGNOSIS OF WHOOPING COUGH AND THE USE OF VACCINE AS A PREVENTIVE MEASURE. DR. L. W. SAUER, Evanston, Ill.

The cough plate of Chievitz and Meyer of Copenhagen is a valuable aid in the early diagnosis of whooping cough. Seventeen original papers on the method have appeared in the United States since Madsen delivered the Cutter Lecture at Harvard University Medical School in 1924. A positive plate is conclusive evidence, but negative plates do not exclude the disease. It has been in constant use in private practice by Sauer since 1925, and has been used by the Michigan State Department of Health since 1932. During the past seven years a total of 8 cc. of a specially prepared Bacillus pertussis vaccine (1 cc. containing 10,000 million bacilli), made from recently isolated hemolytic strains grown on Bordet medium prepared with human blood, was injected into about 1,100 older infants and young children. Forty-two of these were subsequently exposed to pertussis in the 45 controls in 29 families, from four months to six years later; no child who had been given an injection contracted typical pertussis; in 2 the disease occurred in an aborted form. One hundred and forty-six who had received injections were casually but intimately exposed to pertussis in the classroom, at play and through other contacts a total of 279 times. One of them, a sturdy girl of nearly 6 years, one year after injection contracted a paroxysmal cough with vomiting and whooping for three weeks; repeated cough plates were positive; her highest white cell count was 11,500, and there was a slight degree of lymphocytosis. Her younger brother and sisters, who had received injections a year previously, escaped. A total of 6 cc. was injected into 400 homeless "cradle" infants before the fifth week of life. All

have since been legally adopted into private homes. Five were subsequently exposed; in 4 the disease occurred in a very mild form; 1 escaped. During the past two years an appreciable number of physicians in various parts of the country have used the approved commercial vaccine and have, as a rule, substantiated its immunizing effect. In 8 instances, however, it apparently failed to protect. Non-refrigeration has a deleterious effect on the antigen. The Michigan State Department of Health's experiment in immunization with a "washed" vaccine made from whooping cough bacilli grown on sheep's blood medium should yield interesting data within the next few years, if the work is checked by satisfactory, nonimmune controls in the families receiving the vaccine. Commercial pertussis vaccines other than those prepared according to the detailed specifications given by Northwestern University Medical School should not be used, unless their manufacturers offer convincing proof of their worth. To date no such evidence exists.

It is concluded that a total of 8 cc. of specially prepared and refrigerated B. pertussis vaccine given bilaterally in three weekly, subcutaneous injections should confer prolonged immunity in a high percentage of young nonimmune children, if administered at least four months before exposure. The best age for immunization is between the sixth and the eighth month and in the third year of life.

LEPROSY IN CHILDREN. DR. M. H. SOULE, Ann Arbor, Mich.

The data relative to the incidence of leprosy in children furnish the only unequivocal evidence to support the belief in the contagious nature of the disease. In practically every instance in which the home environment of afflicted school children was thoroughly investigated an adult with active lesions was detected. As a rule, one finds the widest distribution of the malady among the offspring when both parents are infected, the next widest distribution when the mother is infected and the least distribution when the condition is present only in the father. Childhood is the period of susceptibility; from 40 to 50 per cent of the progeny of leprous parents manifest signs of the disease in later life, while only from 2 to 4 per cent of the cases are due to conjugal infection. Children born of highly infectious parents rarely show clinical signs if removed at birth (within the first hour of life) to a healthy environment maintained by normal persons.

There is no proof of the hereditary transmission of leprosy, as has been suspected by many—a problem which was studied by Danielssen almost a century ago —although the rôle of "inherited" predisposition cannot be lightly dismissed. Hansen's bacillus has been seen in sections of the placenta, but cases of congenital infection are extremely rare.

The diagnosis of incipient leprosy is not easy. The onset is usually so insidious and the disease causes so little discomfort or inconvenience in its early stages that its true nature is not recognized. The cardinal diagnostic feature, anesthesia, is difficult to detect in children, and the paucity of acid-fast organisms in the initial lesions adds to the confusion. For these reasons the distribution of the disease in early life is much greater than the available records indicate. It is also of interest that cases of the childhood type of the infection are evenly divided among boys and girls, but in adults the ratio changes, and a preponderance of males is the rule. As in tuberculosis, many childhood infections must be self-limited.

From present knowledge of the disease it is reasonable to postulate that its ultimate control lies in the segregation at birth of the children of leprous parents.

TETANUS TREATED SUCCESSFULLY BY ANTITOXIN, AVERTIN AND RESPIRATOR: REPORT OF A CASE. DR. PARK S. BRADSHAW, Ann Arbor, Mich.

A boy, 7 years old, was brought to the clinic because of convulsions. Six days before admission trismus developed, involving all the muscles of the back; this was succeeded the following day by generalized muscular rigidity. The night before admission he awakened often with screaming and had a slight generalized convulsive seizure. He had a history of a mild abrasion on the left elbow, which had healed with scab formation without obvious infection. This occurred seven days before admission.

Examination showed a boy of slender frame, moderately well nourished and restless. The muscles showed a slight tonicity. The tuberculin precipitation reaction was normal. The face was drawn, and the patient was unable to open the mouth; there was definite risus sardonicus. The neck showed tetanic spasm, and the position was that of opisthotonos. The entire spine was rigid and painful. The abdomen showed boardlike rigidity. There was marked contracture of the extremities. A healed abrasion was present on the left elbow. Hyperactivity of the tendon reflexes was the only abnormal neurologic finding. All the laboratory findings, including the results of chemical examination of the blood, urinalysis, examination of the spinal fluid and a blood count, were entirely normal.

Sixty thousand units of tetanus antitoxin was given intramuscularly on admission. Codeine and sodium phenobarbital failed to control the spasms after twelve hours. Treatment with avertin was then begun; 250 mg. per kilogram of body weight was given the first day, and similarly large amounts were given daily for the next three days. This drug seemed to control the spasms when complemented with allyl-isopropyl barbituric acid and sodium phenobarbital. Irritation and bleeding of the rectum developed. Intravenous injections of sodium amytal, 3 grains (0.19 Gm.), complemented with paraldehyde and allyl-isopropyl barbituric acid in sufficient doses to control the seizures, were then tried. Respiratory difficulty accompanied by cyanosis soon became the predominant symptom. By the third day in the hospital artificial respiration was necessary. The Drinker respirator was used for twenty-four hours. Because of pulmonary edema the patient was transferred to an oxygen tent. Large amounts of tetanus antitoxin were administered every few hours, given in the continuous intravenous drip which was being used to control dehydration. The patient was fed a high caloric liquid diet through a nasal catheter. Definite signs of improvement were noted on the sixth day in the hospital. All signs of tetanus were gone by the tenth day. The patient was discharged in good condition after five weeks in the hospital.

To summarize the specific therapy, tetanus antitoxin totaling 100,000 units injected intramuscularly and 100,000 units injected intravenously was given. The total amount of sedatives used was: avertin, 12,400 mg. (for the first four days); sodium amytal, 10 grains (0.65 Gm.); sodium phenobarbital, 7 grains (0.45 Gm.); paraldehyde, 40 cc. (from the fifth to the eighth day), and triple bromide, 10 grains as needed (after the ninth day). Morphine sulphate or codeine was given on several occasions.

The interesting features of this case were the excessive doses of sedatives that were given without apparent harmful effect, the massive doses of antitoxin and the use of the Drinker respirator to combat imminent respiratory failure.

FEEDING THE PREMATURE INFANT. DR. HAROLD B. ROTHBART, Ann Arbor, Mich.

The procedure followed in feeding premature infants at the Cook County Children's Hospital is outlined: The infant receives nothing for the first twenty-four hours of life and is then given 2 cc. of weak tea or water. After this, at one and one-half hour intervals, breast milk and weak tea are offered alternately, each being gradually increased so that by the end of the second twenty-four hours the infant is receiving about 15 cc. of milk and 10 cc. of weak tea. From then on the feedings are increased only if the weight becomes stationary or the infant seems hungry and can take more. At no time is the increase more than 1 ounce (28.35 cc.) of breast milk for the entire twenty-four hours. Cod liver oil and orange juice are added after the third week of life. Viosterol is not used as a routine, nor is iron given. Before the infant is sent home he is gradually placed on a formula of evaporated milk, dextrimaltose and water. Diarrhea is controlled by omitting one or two feedings or instituting starvation periods of from eight to twelve hours. Fluids are given subcutaneously, and, when necessary, blood is given intramuscularly.

Most of the infants treated fared well on this regimen. The total mortality for the group studied (274 infants) was 32.5 per cent. Excluding those who died within twenty-four hours, it was 21.6 per cent. The average stay in the hospital was three months, and the average gain in weight was from 3 to 5 ounces (85.05 to 141.7 Gm.) per week.

Two points are stressed: (1) the superiority of breast milk to other types of feedings and (2) the importance of a gradual increase in the quantity of the feedings and only when that increase is deemed necessary.

PYLOROSPASM: REPORT OF A CASE. DR. M. H. WORTH, Ann Arbor, Mich.

The clinical record of an infant 3 or 4 weeks old who showed pylorospasm is presented. The weight at birth was 5 pounds and 10 ounces (2,551.45 Gm.). The patient tolerated large doses of atropine sulphate until the end of the ninth month, when it was discontinued. Gastric lavage with solution of sodium bicarbonate, thick feedings and eleven intramuscular injections of whole blood were also used. The infant made good progress.

It is suggested that allergy may have played a part in the causation of this condition, but no direct evidence of this is available.

UNCOMMON CONGENITAL ANOMALIES. DR. M. COOPERSTOCK, Marquette, Mich.

I. *Miscellaneous Cases.*—The tendency for congenital anomalies to occur multiply is well recognized. The obvious presence of one anomaly should stimulate a search for others. Occasionally an infant is born with an unusually large number of congenital abnormalities, as is illustrated by the following cases:

CASE 1.—A premature infant has harelip, cleft palate, absence of both thumbs, bilateral fusion deformity of the humerus and ulna, bilateral clubfeet and hypospadias.

CASE 2.—An 8 year old girl has marked spina bifida occulta. Roentgenologic examination confirmed this condition and revealed the presence of total situs transversus.

CASE 3.—A 12 year old boy has rigidity of the neck, which has been present since birth. Roentgenograms show fusion of the occipital bone with the atlas and ankylosis of the atlas with the axis.

CASE 4.—A 5 year old girl has a striking congenital abnormality of the spine out of all proportion to the physical findings. At first glance the x-ray films suggest the presence of a double spine. Close inspection of the roentgenograms reveals evidence of complete lack of fusion of the two halves of the entire vertebral mass from the eighth to the twelfth thoracic vertebra and the entire group of lumbar vertebrae, with secondary fusion of various hemivertebrae. In addition, there is spina bifida occulta of fairly marked degree involving the entire sacrum. There is also bilateral anomalous fusion of the posterior ends of the tenth and eleventh ribs. Clinically, the patient shows only a moderate degree of dorsolumbar scoliosis. No neurologic findings of a pathologic nature could be demonstrated. The actual position of the spinal canal and the spinal cord is a matter of great interest and conjecture.

II. *Congenital Hypertrophy of Extremities.*—This includes congenital lymphedema, which may be divided into (*a*) the simple type and (*b*) the familial type (Milroy's disease); arteriovenous fistula, and congenital lymphedema of extremities associated with total unilateral hypertrophy.

CASE 1.—E. R., a girl, 3 years old, has been observed since early infancy because of an enlarged left leg. There is no detectable increase in the length of the extremity. The hypertrophy involves only the soft tissues and does not extend above Poupart's ligament. There is no pain or pitting on pressure, and the swelling is firm. Roentgenologically, there is no difference in the size or density of the long bones of the lower extremities.

CASE 2.—A boy, 18 months old, a brother of E. R. (case 1), presents a less noticeable enlargement of the right lower extremity. Roentgenograms show a slight but definite increase in the length of the tibia and fibula. There is also a discernible increase in the soft tissues. There is no definite evidence of the existence of an associated arteriovenous communication.

The condition in the first case corresponds to simple congenital lymphedema, which is produced by developmental dilatation of the lymphatic vessels, designated

as lymphangiectasis. The term elephantiasis is used to connote a chronic condition resulting from lymphedema characterized histopathologically by hypertrophy of the skin and subcutaneous connective tissue. The occurrence of a congenitally enlarged limb in this patient brings up the question of the possibility of Milroy's disease. These two forms of congenital hypertrophy, simple and familial, do not differ essentially, except in the fact of hereditary transmission. While lymphedematous swelling is present in both children, in the case of the brother there is an associated increase in the size of the long bones of the involved extremity, a finding usually not included among the criteria for Milroy's disease. No other members of the family are known to have a similar condition.

CASE 3.—E. S., aged 12 years, shows a good example of congenital hypertrophy of an extremity due to the presence of an arteriovenous fistula; this involves the right lower extremity. The arteriovenous communication is located in the right inguinal region. The following tabulated summary shows the chief diagnostic signs of arteriovenous fistula, together with the findings for this patient:

General hypertrophy of affected part	Present
Roentgen evidence of advanced bone growth	Present
Hemangiectasis-phlebarteriectasia	Present
Elevated surface temperature of affected part	2.6 F. difference
Increased oxygen saturation of venous blood of affected part	Not determined
Peripheral thrill and bruit	Present
Blood pressure (increased systolic, decreased diastolic, general diastolic pressure decreased)	
Systolic: Right leg, 135; left leg, 98; right arm, 102; left arm, 98	
Diastolic: Right leg, ?; left leg,?; right arm, 60; left arm, 50	
Bradycardiac reaction	Lowering of 22 beats with manual obliteration of the fistula
Cardiac hypertrophy	Present

CASE 4.—E. B., a boy, aged 11 years, presents a ponderous right upper extremity. The right hand is particularly large and is broad and spadelike. No evidence of an associated arteriovenous fistula could be found. While the long bones of the arms reveal only a slight difference roentgenographically, there is marked variation in the size of the metacarpal bones of the right hand, which is especially pronounced in the metacarpus of the forefinger.

True total unilateral hemihypertrophy is relatively rare, only 56 instances having been reported. It should be considered in the differential diagnosis in cases such as those described in group II. The etiologic factors are not known.

INFLUENZAL MENINGITIS TREATED WITH ANTI-INFLUENZAL SERUM: REPORT OF A CASE. DR. HARRY A. TOWSLEY, Ann Arbor, Mich.

Four main principles were followed in the treatment in this case: (1) repeated lumbar punctures to remove spinal fluid and any organisms it contained; (2) the injection of air into the spinal canal to aid in the prevention of adhesions, which are reputed to be of common occurrence in influenzal meningitis; (3) repeated transfusions of small amounts of adult's blood, following the observations of Fothergill and Wright that adult's blood has a bactericidal power against Bacillus influenzae which is not present in infant's blood and is of lesser power in children's blood and (4) the use of anti-influenzal serum (Park), which was used successfully in three cases of influenzal meningitis with recovery, reported by Neal, Jackson and Appelbaum in 1933. To this serum fresh complement was added on four occasions.

J. R., a girl, aged 7 years, had a severe headache and projectile vomiting twelve days after muscle transplant for the correction of polioparalysis of the left forearm of long standing. She was admitted to the contagious unit on Sept. 14, 1934, with meningitis. Fifty cubic centimeters of turbid spinal fluid was removed, and 30 cc. of antimeningococcic serum was given intraspinally. A second lumbar puncture was done on the evening of admission, and 20 cc. of antimeningococcic serum was given. No organisms were seen in direct smear. The following morning the culture revealed B. influenzae. The organisms were immediately

Record of Daily Treatment

Day of Disease	Cc. of Spinal Fluid Removed	Cc. of Serum Injected Intraspinally	Cc. of Serum Injected Intramuscularly	Cc. of Air Injected	Cell Count of Spinal Fluid	Report on Culture	Cc. of Fluid (5% Dextrose in Physiologic Solution of Sodium Chloride) Injected Intravenously	Cc. of Blood Given
	50.0							
1	50.0	30, antimeningococcic	.....	..	.....	.....	600	
	25.0	15, antimeningococcic	15, antimeningococcic	..	5,140			
	18.0	10, anti-influenzal	10, anti-influenzal	16	.....	Positive	1,250	
2	35.0	20, anti-influenzal	10, anti-influenzal	15	.....	Positive		
	45.0	20, anti-influenzal	.....	..	.....	Positive	500	
	50.0	20, anti-influenzal	.....	15	.....	Positive		
3	45.0	20, anti-influenzal	.....	10	3,490	Positive		
	45.0	10+5, anti-influenzal; complement added*	.....	10	3,470	Positive		
4	28.0	10+5, anti-influenzal; complement added	.....	10	.....	Positive	.....	200
	48.0	6+5, anti-influenzal; complement added	.....	12	1,820	Positive		
5	60.0	20, anti-influenzal	.....	..	.....	Positive		
	26.0	.....	.....	10	.....	Positive		
6	15.0	.....	.....	4	.....	Positive		
	60.0	.....	.....	15	5,930	Positive		
7	35.0	20+10, anti-influenzal; complement added	.....	5	5,540	Positive	.....	190
	35.0	20+5, anti-influenzal; complement added	.....	..	.....	Positive		
8	2.0	.....	.....	2	.....	Positive		
9	4.0	.....	20, anti-influenzal	..	1,105	Positive	2,500	
10	0.1	.....	20, anti-influenzal	..	.....	Positive	2,000	
11	50.0	30, anti-influenzal	10, anti-influenzal	..	.....	Negative		
12	3.0	.....	10, anti-influenzal	..	.....	Negative		
13	39.0	10, anti-influenzal	.....	..	1,210	Negative		
14	30.0	.....	.....	..	480	Negative		
15	1.0	.....	.....	4	.....	Negative	1,250	
16	29.0	.....	20, anti-influenzal	..	.....	Negative		
17	15.0	.....	.....	..	210	Negative		
18	15.0	.....	.....	..	.....	Negative	...	230
30	4.0	.....	.....	..	100	Negative		
Total	862.1	45, antimeningococcic 206, anti-influenzal	15, antimeningococcic 100, anti-influenzal	128			8,100	620

* 10+5 = 10 cc. serum + 5 cc. complement.

agglutinated by the antiserums in dilutions up to 1:320. Slow agglutination took place in dilutions up to 1:640, being completed in this dilution at the end of ten minutes. The record during treatment is shown in the table.

The temperature was of a septic type, ranging from 99 to 103 F. daily, until the ninth day of the disease. From the ninth to the nineteenth day it reached 102 F. on but six occasions and then only a few hours at a time. From the twentieth to the fifty-second day it remained at approximately 99 F.

From the third through the eighth day of the disease lumbar puncture was done twice daily, and from the ninth through the eighteenth day, once daily. On four occasions during this period only small amounts of fluid could be obtained. A block was feared. However, the patient's condition was no worse on those days, and the fundi did not appear abnormal. Continuous intravenous injections of fluids were given; heat was applied to the lumbar region, and on the following days adequate amounts of fluid could be obtained by lumbar puncture.

On the fourth day after specific treatment was instituted the spinal fluid cultures became negative and remained so. Intraspinal injections of serum were discontinued on the thirteenth day of the illness, and intramuscular injections on the sixteenth day. On the thirtieth day the patient complained of severe headache in the right frontal region. There were no other neurologic findings. Lumbar puncture was done, and 4 cc. of clear fluid was removed. The cells numbered 100 per cubic centimeter; 90 per cent were lymphocytes.

Forty-five days after admission the patient was permitted to walk. The gait was somewhat ataxic, but gradually improved and sixty days after admission was normal. There were no noticeable abnormalities in the child's conduct.

Examination of the blood on September 14 showed 78 per cent hemoglobin and 38,600 white cells, 93 per cent of which were polymorphonuclears and 7 per cent lymphocytes. On October 1 the white cells numbered 14,400. The urine was essentially normal. Chemical examination of the spinal fluid on September 14 showed 25 mg. of sugar per hundred cubic centimeters and 640 mg. of chlorides. On September 15, examination of the spinal fluid revealed a trace of sugar. Examination of the blood showed 119 mg. of sugar per hundred cubic centimeters.

VENOCLYSIS AS A THERAPEUTIC AGENT IN THE INFECTIOUS DIARRHEA OF INFANCY.
DR. PARK S. BRADSHAW, Ann Arbor, Mich.

Since Karelitz and Schick published their first paper on the use of the continuous intravenous drip for toxicosis in infants in 1931, a great many pediatric clinics have successfully used similar procedures and reported definite lowering of their mortality statistics for this type of case.

My series of 40 cases of infectious diarrhea does not represent the average run of cases of diarrhea. The patients were selected for this type of therapy because they were dying or because all other methods of administration of fluid had failed to bring about improvement. These extreme cases were observed in three different clinics: the children's department of the Cincinnati General Hospital, the Cincinnati Children's Hospital and the infant's ward of the University of Michigan Hospital. They are not limited to an epidemic or to a definite locality. They should, as a consequence, be fairly representative of the severe diarrheas of infancy seen in every large city during the summer months.

The technic used was almost identical with that recommended by J. M. Brush of Brooklyn, whose apparatus was used in two of the clinics. An added refinement consisted of the incorporation of a two-way stop-cock 6 inches (15.24 cm.) from the patient's foot, thus allowing for the easy flushing of the apparatus and the injection of blood without disturbing the cannula, which was covered by a sterile dressing.

Fluid was allowed to enter the patient's foot at the rate of from 10 to 15 drops per minute. A 10 per cent solution of dextrose given alternately with a 5 per cent solution of dextrose in Hartman's solution were the fluids used. Citrated blood to the extent of 10 cc. per pound (0.5 Kg.) of body weight was given on repeated occasions to all patients failing to show immediate improvement under

the fluid therapy. The problem of keeping the fluid warm was disregarded in view of its slow entrance into the patient's vein. The drip was continued until the stools showed definite improvement in character and number and until the patient was able to take fluids by mouth. This period varied in our cases from several hours to seventeen days. No food or fluids were given by mouth for from twelve to twenty-four hours, after which small quantities of protein milk was offered at widely spaced intervals.

Edema of the legs occurred in practically all our cases. It became evident about the fifth day and subsided spontaneously in every case with the cessation of the drip, as did the phlebitis which occurred in several cases. By mistake, more than 200 cc. was allowed to enter one patient's vein within an hour. This resulted in generalized edema. Chemical examination of the blood at this time showed: total protein, 4 mg. per hundred cubic centimeters; albumin, 2.66 mg.; globulin, 1.34 mg.; calcium, 6.5 mg.; phosphorus, 1.95 mg., and chlorides, 91 mg. The patient recovered.

Of the 40 patients studied, 20 died—a mortality of 50 per cent. Of these, 16, or 80 per cent, had a parenteral infection, which was respiratory in 10, or 62 per cent; 7, or 43 per cent, had otitis media; 1 had lead poisoning, and 1 had pyelitis. Of the 20 who recovered, 10, or 50 per cent, had a parenteral infection, which was respiratory in 3, or 30 per cent; 4, or 40 per cent, had otitis media; 1 had thrush; 1 had impetigo and 1 had generalized furunculosis. Each of the entire group showed at least temporary improvement after from 500 to 1,000 cc. of the fluid had been given. The disappearance of the dehydration and the increased tolerance for fluids given by mouth were the two most striking clinical observations. The treatment seemed less effective in infants with a severe respiratory infection, particularly pneumonia.

Dangers from this method may arise from too rapid or too irregular flow of the fluid, from the development of phlebitis, from dilution of the blood proteins and from circulatory failure.

LIBMAN-SACKS SYNDROME: REPORT OF A CASE. DR. G. H. BELOTE, Ann Arbor, Mich., and DR. H. S. V. RATNER, Ann Arbor, Mich.

A preliminary report of a case of Libman-Sacks syndrome in a girl of 7 years is given. The clinical course and the characteristic verrucous valvular lesions described by Libman and Sacks are present in this case. Detailed studies, with particular reference to the cutaneous manifestations and the etiology, are in course of publication. This is the first case to be recorded outside New York City.

HYPOGLYCEMIA IN CHILDREN: REPORT OF A CASE. DR. JOSEPH C. JAUDON, Ann Arbor, Mich.

A brief review of the many symptom complexes associated with hypoglycemia is given. Emphasis is placed on the observations of Josephs and Griffith, namely, the occurrence of the attacks early in the morning after a brief period of starvation and the relief of symptoms following therapy, as aids in diagnosis. A low blood sugar content in itself is not diagnostic.

A brief résumé of the case is presented: J. M., a white boy, aged 2 years and 9 months, was admitted to the pediatric department of the University of Michigan Hospital on Aug. 23, 1934. During the previous year he had had frequent severe convulsions lasting from twenty minutes to one hour. The seizures had never occurred at any time other than between the hours of 2:00 and 7:00 a. m. Because of the severity and frequency of the convulsions hospitalization was occasionally necessary. Between attacks the child was apparently normal in every respect. He had a craving for sweets. Supper was served at 5:00 p. m. and breakfast at 8:00 a. m.—a relatively long period of starvation. Aside from an acute infection of the upper respiratory tract, the routine physical examination gave negative results. The results of neurologic, roentgen and laboratory studies were essentially normal.

Early in the morning following admission the patient had twitchings of the left arm and leg and of the face; he became unconscious, had markedly dilated pupils and perspired profusely. This was followed by a severe clonic movement of the right arm and leg, which gradually spread to the left side. Respirations became irregular. Marked tachycardia associated with cyanosis of the lips and nail beds was noted. By the time that dextrose was available for intravenous administration he was well over the attack. He remained drowsy for some time but eventually recovered spontaneously. During the attack the blood sugar was 30 mg. per hundred cubic centimeters, and the blood calcium, 14.5 mg. The calcium was considered normal, in view of the fact that large daily doses were prescribed because of suspected tetany. The dextrose tolerance test showed no abnormality, aside from a relatively low blood sugar content of 60 mg. during fasting.

The patient was readmitted on November 1. Through some misunderstanding he was allowed to continue his usual routine diet and did not receive the therapeutic trial of frequent feedings of easily assimilated carbohydrate while at home. The convulsions continued with the same frequency and severity. A dextrose tolerance test on November 2 revealed a low blood sugar content during fasting and three hours after a meal. The blood sugar content was 53 mg. per hundred cubic centimeters during fasting, 204 mg. thirty minutes after a meal, 208 mg. one hour after a meal, 121 mg. two hours after a meal and 62 mg. three hours after a meal. Breakfast was delayed, along with that of another boy of approximately the same size and weight. Two units of insulin was given each child at 9:00 a. m. About 11:00 a. m., while the patient was being exhibited in Dr. Cowie's senior clinic he had an attack similar to, but less severe than, the one noted on his first admission. Three minims (0.18 cc.) of epinephrine hydrochloride was administered subcutaneously, and within less than two minutes the patient was sitting up in bed perfectly conscious and apparently normal.

The insulin test was repeated within a few days, and similar results were obtained. During the last convulsion the blood sugar content was 43 mg. per hundred cubic centimeters. Within two minutes after the injection of epinephrine hydrochloride it had risen to 54 mg.—a figure above the level at which symptoms were noted in this patient. The control patient did not experience the slightest effect from the insulin. At the time of discharge the child was receiving extra feedings of carbohydrate and not only has had no attacks but feels better than he has felt for some time.

The treatment consists, first, in shortening the relatively long period of starvation between the evening and morning meals; second, in inducing a higher blood sugar content during the period when it is known to fall the lowest, and, third, in offering immediate relief by carbohydrates or epinephrine hydrochloride when the attack occurs. Sweetened orange juice should be taken before retiring and on rising in the morning. A dose at midnight may be necessary. Sweets should not be prohibited. Chocolate bars, bread and jelly, Karo water and similar foods may be taken in small quantities between meals. Parents should be instructed in the use of epinephrine hydrochloride during the attack (from 3 to 5 minims [0.18 to 3 cc.] should be given), but candy, sugar or orange juice should usually be sufficient.

Surgical intervention is said to have a definite place in a small percentage of these cases. Reference is made to Marriott's report of an infant with hypoglycemia in whom all conservative methods of treatment failed to prevent convulsions. Subtotal pancreatectomy apparently cured the patient.

MYASTHENIA GRAVIS IN A BOY NINE YEARS OLD. HAROLD B. ROTHBART, Ann Arbor, Mich.

The disease in this boy started at 6 weeks of age, with weakness of the ocular muscles and drooping of the eyelids. Walking was not delayed, but the gait was always awkward. Since infancy he has had a nasal twang, weakness of the muscles of both sides of the face and "asthmatic" attacks, which have become less frequent since 2 years of age and are now characterized by gurgling sounds

in the throat during sleep. Generalized muscular weakness and fatigability which improves on rest have been the dominant features. The signs and symptoms are least marked in the morning on rising, but increase in degree as the day progresses. Within the past year there has been a progression in the severity of the symptoms. There was no illness preceding the onset of this disease, though the patient has been subject to many colds since, mainly in the winter months.

A brother of the patient, now 13 years old, was similarly affected; the symptoms appeared when he was 6 months old, following an infection of the upper respiratory tract. Though his clinical picture was almost entirely similar to that of this patient, he has shown a steady spontaneous improvement since the age of 7 years. At present he presents only bilateral lagophthalmos and external ophthalmoplegia. Another brother, now 18 years old, had lagophthalmos when 2 years old, during whooping cough, which cleared up after the whooping cough subsided, but which even now shows a tendency to recur with any acute illness. One brother died of pneumonia about twenty years ago at the age of 7 months. During the pneumonia he showed well developed drooping of both eyelids and weakness on sitting up.

In the case reported physical examination showed extensive muscular weakness, paresis of both sides of the face, external ophthalmoplegia, cycloplegia, lagophthalmos, a nasal twang, a waddling gait and lordosis, several carious teeth and septic tonsillar tags. The myasthenic reaction of Jolly was absent. Examination of a section of the triceps muscle revealed no pathologic changes. Chemical examination of the blood, including the dextrose tolerance test, gave normal results. The basal metabolic rate was —9 per cent. The urinary creatinine was low normal while the patient was on a meat-free diet, while the creatine was about one and a half times normal. Roentgenograms of the skull, chest and long bones were normal. There was no enlargement of the thymus. The lower extremities show bilateral coxa valga, which has also been noted in other muscular dystrophies.

The patient was treated with glycine and ephedrine. To date, one month after therapy was begun, he has shown striking improvement. He feels much better and stronger, and the parents have noted that he does not tire so readily and can keep his eyes open for a much longer time.

STATUS OF ENDOCRINE RESEARCH IN 1934. DR. E. A. SHARP, Detroit.

I. Predemonstration phase
  (*a*) Pineal gland
II. Demonstration phase
  (*a*) Intestinal tract
    (1) Cholecystokinin
    (2) Duodenal hormone
  (*b*) Anterior lobe of pituitary gland
    Adrenotropic, fat-metabolizing, pancreatropic, parathyrotropic and diabetogenic principles have been claimed
  (*c*) Thymus
III. Concentration phase
  (*a*) Parathyroid
  (*b*) Anterior lobe of pituitary gland
    (1) Gonadotropic
    (2) Thyrotropic
    (3) Lactogenic
    (4) Growth-promoting hormones
  (*c*) Adrenal cortex
IV. Isolation and analysis phase
  (*a*) Intestinal tract (secretin)
  (*b*) Posterior lobe of pituitary gland
    (1) Alphahypophamine
    (2) Betahypophamine

(*c*) Testis
(*d*) Pancreas (insulin)
(*e*) Corpus luteum (Progestin)
(*f*) Ovary
(1) Theelin
(2) Theelol

V. Synthetic phase
(*a*) Adrenal medulla (epinephrine)
(*b*) Thyroid (thyroxine, a derived principle)
(*c*) Ovary (theelol converted into theelin)

The outline shows the status of endocrine research in 1934. The primary object of Kamm of Detroit, who devised this concise method of illustrating progress in research, was to show by yearly comparisons the actual chemical status of each gland and hormone.

Glands regarded as possessing definite incretions, awaiting demonstrable evidence, are placed in phase I. As knowledge concerning them increases they are advanced to the other phases. At the close of 1934 there is a concentration of incretory structures undergoing laboratory (and also clinical) demonstration. Doubtless before another year has elapsed purification and stabilization will advance some of them to phase III.

It is worthy of note that crystallization of the male sex hormone and of the corpus luteum factor has been reported. They will be eligible for advanced classification after the original work has been confirmed. Adrenal cortex hormone has also been isolated, according to evidence submitted during the closing months of 1934, which will change its status in the near future if confirmatory evidence is adduced.

RELATION OF THE ANTERIOR LOBE OF THE HYPOPHYSIS TO GROWTH AND DEVELOPMENT. DR. ROBERT L. SCHAEFER, Detroit.

The cytologic structure of the anterior lobe of the hypophysis cerebri consists of three types of cellular elements: the chromophobe, the function of which is unknown; the eosinophilic cell, believed to be concerned in the elaboration of the growth factor, and the basophilic cell, to which is ascribed production of the sex hormone.

Clinical prototypes of dysfunction of both the sex and growth factors are met with in endocrine medicine.

1. Hypofunction of the eosinophilic cell results in pituitary dwarfism, which is characterized by a proportionate type of undergrowth. This is determined principally by mensuration: the span; the upper measurement, from the symphysis to the vertex of the head, and the lower measurement, from the symphysis to the soles, which are all approximately equal. This in itself is sufficient to differentiate pituitary dwarfism from the disproportionate forms of dwarfism. A patient with this condition is a miniature replica of the normal person. Treatment consists of replacement by injection of an adequate amount of growth hormone from the anterior lobe of the pituitary gland. Because of frequent secondary hypothyroidism associated with this condition, as much desiccated thyroid extract as the patient can tolerate is also indicated.

2. Hyperfunction of the eosinophilic cell before adolescence results in a reverse picture of pituitary dwarfism—proportionate or pituitary gigantism. In this instance the measurements cited are all greater than the maximal normal measurements, but, too, are proportionate. If this hyperactivity occurs after adolescence and sexual maturity, which is coincident with epiphyseal closure, typical acromegaly occurs. For the preadolescent patient no therapy is suggested. For the postadolescent patient radiation or surgical removal of the hypophysis is indicated.

3. The most frequent and important type of hypopituitarism is the clinical syndrome known as adiposogenital pituitarism, or Fröhlich's disease. In this

entity the hypofunction relates principally to the sexual factor, and the condition is characterized by a particular type of obesity which is confined to the pectoral and pelvic girdles and the regions of the mammary glands and the mons pubis, aplasia of the external genitalia and, frequently, cryptorchidism. Treatment of patients with this condition is most satisfactory and consists of stimulation of delayed sexual development by the judicious use of the anterior lobe pituitary-like hormone and also control of the obesity by diet, and, wherever indicated and tolerated, desiccated thyroid extract.

4. A rare but interesting entity attributable to complete deficiency of the anterior lobe of the pituitary gland is known as Simmond's disease. In this condition statural measurements, weight and sexual development are all subnormal. The skin is of the presenile type, being inelastic and excessively wrinkled. Arcus senilis is occasionally found. Replacement therapy is indicated here in the form of a suitable whole extract of the anterior lobe.

ENDOCRINOPATHIES RELATED TO THE THYROID DURING INFANCY AND CHILDHOOD. DR. JOHN L. LAW, Ann Arbor, Mich.

Endocrinopathies associated with the thyroid gland have an experimental and clinical background which affords some of the most clearcut clinical entities and therapeutic possibilities in the field of endocrinology.

Early diagnosis and treatment are essential if irreparable damage to the infant is to be avoided. Roentgen evidence of delay in the appearance of the epiphyseal centers and a high blood cholesterol content are important criteria. The phase angle measured by electrical conductivity, which is said to be specific for disorders of the thyroid, and the determination of the insensible loss of weight may prove to be of diagnostic importance, if suitable standards are ascertained, as a measure of the metabolic rate in early cretinism. The differentiation of juvenile myxedema from cretinism is important. Thyroid therapy may sometimes fail in cretinism, but it is uniformly successful in myxedema.

Hypothyroidism of low degree is not infrequently overlooked. It usually occurs in the teens and is more frequent in girls. Ease of fatigue, constipation, apathy, retarded mental processes and a tendency to gain weight should be suggestive evidence. The basal metabolic rate is low, in most cases minus 20 per cent. The giving of from ⅛ to ¼ grain (0.008 to 0.016 Gm.) of dried thyroid extract twice a day usually causes the disappearance of symptoms. Therapy should be continuous over long periods, or a relapse may occur.

The incidence of simple colloid goiter is about one fifth of what it was before the importance of iodine in the function and structure of the thyroid gland was shown by Marine and other workers. In Michigan iodized salt is used in foods as a prophylactic. The incidence of goiter in school children has been reduced from 35 to 1 per cent since its introduction.

Hyperthyroidism, or exophthalmic goiter, is uncommon in children. The cardinal signs of this disease are the same as in adults. The iodine therapy and surgical measures are also the same.

There is an interrelationship of the thyroid to the other endocrine glands in children. Hypopituitarism induces atrophy of the thyroid, and hyperfunction of the adrenals induces hyperfunction of the thyroid, which may be overcome, as Crile has shown, by denervation of the adrenals. Both conditions are amenable to appropriate treatment. Removal of the thyroid gland in animals results in enlargement and increased secretion of the pituitary gland, and the injection of the acid extracts of the anterior lobe of the pituitary gland causes enlargement of the thyroid. Increase in secretion of the thyroid diminishes the limit of assimilation for sugar; the opposite effect takes place on removal of the thyroid gland.

EFFECT OF POLLEN THERAPY ON CUTANEOUS REACTIONS IN RELATION TO THE RELIEF OF SYMPTOMS. DR. SAMUEL J. LEVIN, Detroit.

In 87 cases of pollen hay fever and asthma in which the patients were treated during the past summer (1934) skin tests were done by the scratch method before and

after treatment to determine the effect of specific pollen therapy on cutaneous sensitivity. About one third of these patients were children. Only the cases in which the fall group of pollens were the allergic agents are included. The patients were treated with a mixed extract of ragweed. The children received as a final dose an average of 1 cc. of a 3 per cent extract (30,000 units), and the adults, an average of 2 cc. of a 3 per cent extract (60,000 units). About twenty-three injections were necessary to attain the final dosage, which was continued at weekly intervals throughout the season of pollenization.

Ninety-four per cent of the patients obtained from very good to complete relief. All but 2 of these showed marked diminution in their cutaneous reactions. In approximately 85 per cent of the patients with initial four plus reactions these were reduced to slightly positive or negative reactions. In 60 per cent the initial three plus reactions these were reduced to slightly positive or negative reactions.

In only 2 of the patients in whom the cutaneous reactions were reduced to slightly positive or negative reactions were the results other than good, and the majority of patients were completely free from reactions. In 2 patients no change was noted in a three plus reaction that was present at the beginning of treatment, yet these patients had very good results. Poor results were obtained as follows: In 1 patient the reduction was reduced from three plus to slightly positive, in another from three to two plus and in a third from four to two plus.

This study seems to indicate that marked diminution of positive cutaneous reactions by specific pollen therapy is in the majority of cases associated with marked clinical benefit.

STANDARDIZATION OF ALLERGIC ANTIGENS FOR INTRADERMAL TESTING AND TREATMENT. DR. D. MURRAY COWIE, Ann Arbor, Mich., and DR. EMMA WARDELL, Ann Arbor, Mich.

The importance of standardization of antigens seems great. Analyses of a large number of dry powdered "proteins" to determine their nitrogen content showed variations of from 0.95 to 0.01 mg. per hundred cubic centimeters with saline extracts and from 0.92 to 0.021 mg. with water-alcohol extracts. Serial curves for cutaneous reactions show that an antigen with a nitrogen content of 0.95 mg. per hundred cubic centimeters gives a much larger reaction than when the nitrogen content is reduced to 0.05 mg. The antigen of the same protein with a nitrogen content of 0.05 mg. per hundred cubic centimeters gave a satisfactory clinical reaction in a sensitive person. A point was reached in the dilution of all the antigens above which it was not necessary to go in order to secure satisfactory and comparable reactions. At present the concentration is placed at 0.05 mg. per hundred cubic centimeters. The largest reaction obtained with this dilution was 42 mm.; the smallest, 10 mm. Many antigens have a much lower nitrogen content—as low as 0.01 mg. per hundred cubic centimeters. These antigens have always given cutaneous reactions. They can be concentrated to the standard of 0.05 mg., but this does not seem necessary. On the other hand, some antigens of a strength of 0.05 mg. do not give satisfactory cutaneous reactions when diluted to a concentration of 0.01 mg.

In the preparation of solutions of antigen the greatest precautions against chemical as well as bacterial contamination must be taken, particularly with reference to glassware and distilled water. In testing, contamination of the needle and syringe easily occurs. The tendency to omit control testing may be responsible for error. The control must be prepared with great care. For example, one control reaction showed a 40 mm. reaction at one-quarter hour, a 30 mm. reaction at one-half hour, a 5 mm. reaction at one hour, and a 4 mm. faint reaction at four hours. When the test was repeated, using an especially clean, sterile syringe and a dry needle, the reaction was 15 mm. at one-quarter hour, 2 mm. at one hour and a very faint reaction at four hours. When one is testing many patients in a day a safe method is to use a separate syringe for each antigen and a new sterile dry needle for each test. The size of the dose should also be standardized. Three hundredths of a cubic centimeter seems satisfactory, but indications seem to be that even this dose may be larger than necessary.

PRESERVATION OF ALLERGIC ANTIGENS AGAINST BACTERIAL CONTAMINATION AND CHANGE IN COLOR; THE PREVENTION OF IRRITATION OF THE SKIN INDUCED BY INTRADERMAL TESTING. DR. MERYL M. FENTON, Ann Arbor, Mich.

Since the inception of allergy as a special field of medicine the problem of preservation of the protein extracts used in testing has received considerable attention. This has been more pronounced since intradermal testing has become so popular. In general, one of the derivatives of creosote is commonly used as the chemical antiseptic. Glycerin has proved a satisfactory preservative for pollens since it was first used by Clark in 1917. This observation has been substantiated by several workers, notably Clock, who advocated 66.6 per cent concentration with a 33.3 per cent saturated solution of sodium chloride, and Aaron Brown, who investigated the use of a 50 per cent solution of glycerolated extracts. The latter are desirable for purposes of therapy because of lack of deterioration of the solutions and slowness of absorption, thus minimizing the chances of a constitutional reaction. For intradermal testing, however, glycerolated extracts have been found to be excessively irritating.

Rappaport of Chicago has demonstrated the disadvantages of Berkefeld filters and chemical sterilization for use in the sterilization of all proteins. He proposed a method of sterilization by dry heat, but this was found to be unsatisfactory because of the time consumed and the technical difficulties involved.

Protein extracts prepared with a 14 per cent solution of alcohol and distilled water are satisfactory from a bacteriologic point of view, but they have been found to be very painful when injected intradermally. In intradermal testing, the degree of reaction is determined by the extent of the wheal and the area of erythema at the site of injection. We have found this local reaction to be definitely altered by the alcohol itself in certain persons. In an effort to find a suitable substitute, several preservatives, including glycerin, phenol, merthiolate and the methyl ester of parahydroxybenzoic acid were studied. The first was soon discarded when its disadvantages were demonstrated. The proteins prepared with Coca's solution (sodium chloride, 0.5 per cent; sodium bicarbonate, 0.275 per cent, and phenol, 0.4 per cent) and merthiolate 1:10,000 at first proved satisfactory. Pain was eliminated. But many of the solutions soon showed signs of chemical change by turning brown after from two to three months, probably due to a reaction with the sulphur radical present. Phenol also caused discoloration with some antigens. These solutions did not keep so well as those prepared with alcohol. Extracts that are naturally brown, such as the epidermals banana, tobacco and pepper, do not turn darker when the methyl ester of parahydroxybenzoic acid is used as the preservative.

Several antigens were then prepared with an 0.85 per cent solution of sodium chloride and a 0.1 per cent solution of the methyl ester of parahydroxybenzoic acid. These extracts have been satisfactory from a bacteriologic and antigenic standpoint. They are painless on injection and cause no untoward pseudoreactions. They should prove highly satisfactory in carrying out sensitization examinations.

SODIUM SALICYLATE GIVEN INTRAVENOUSLY IN THE TREATMENT OF ALLERGIC PATIENTS. DR. B. JIMENEZ, Ann Arbor, Mich.

For many years we have been using sodium salicylate given intravenously in our sensitization clinic for the nonspecific treatment of patients with hay fever who come in too late for specific treatment, for those whose specific treatment has not been adequate and for patients with other allergic conditions, such as urticaria, asthma and eczema. This method of treatment has been of great help in the care of many of these patients.

The treatment consists in the intravenous injection of 5 cc. of a 20 per cent solution for children up to 5 years old, adding 1 cc. per year until the dose of 15 cc. for adults is reached. The injections are given very slowly with the patient lying down. Great care should be taken to be sure that no fluid gets into the adjacent tissues. It must always be determined whether the patient has any idiosyncrasy in regard to salicylates. The patients usually complain of painful

sensations in the vein, hands, feet or shoulders, which last only a few seconds. If a small vein is used the treatment is more painful. Some patients may feel warm, hot and dizzy for a few minutes; others say that they feel drowsy or "peculiar" for two or three hours. No unfavorable reactions have occurred (591 injections have been given patients). Two patients had hives, 1 for two hours; 6 had vomiting, and in 2 menstruation was precipitated. The vein is almost always reddened for a few days. The same vein is never used twice.

I present a series of 235 cases of hay fever and 20 cases of such allergic manifestations as urticaria, asthma and eczema.

The duration of relief from symptoms following the injection varied from a few hours to one week. A few patients required not more than two injections during the season.

RELATIONSHIP OF GENERAL REACTION TO LOCALIZED REACTION IN SENSITIZED PERSONS FOLLOWING AN INJECTION OF SPECIFIC ANTIGEN. DR. WILMA SACKS, Ann Arbor, Mich.

Because of certain theoretical considerations suggested by the work of Kahn on tissue immunity, it was decided to study the relationship between local reactions and the occurrence of general reactions in the course of specific pollen extract treatment for hay fever in Dr. Cowie's Clinic. About 200 cases were studied. The patients included both children and adults. It was found that about 30 per cent of the number had no general reactions during the course of treatment. A high percentage of these were children and adolescents. In the group having general reactions there was great variation in the number and severity of the reactions. In both groups the local reactions varied greatly, from no visible redness to areas 6 inches (15.24 cm.) in diameter or swelling and redness of the entire arm. From the reactions of this group of patients during long series of treatments, it was concluded that there is no definite relation between the size of the local reaction and the occurrence of general reactions in the course of specific therapy for hay fever.

EXPERIMENTAL ACUTE POLIOMYELITIS IN MONKEYS: CLINICOPATHOLOGIC OBSERVATIONS. DR. D. MURRAY COWIE, Ann Arbor, Mich., and DR. K. LOWENBERG, Ann Arbor, Mich.

We produced typical acute poliomyelitis in monkeys by intracerebral inoculations of Flexner cord virus. The incubation period was 3, 4, 5, 9 and 22 days, respectively. The onset was usually sudden, with prostration, fever, muscular weakness or paralysis. The dromedary phenomenon was observed in one monkey. The following clinical symptoms were observed: elevation of temperature to from 102 to 104.3 F., headache, restlessness, excitability, grinding of the teeth, twitching, watering of the eyes, shivering, tremor, convulsions, diarrhea, constipation, shallow breathing, awkwardness, muscular stiffness, muscular weakness and sudden, gradually progressive and extensive paralyses, usually initiated by general weakness, progressing to palsy which was transient or permanent. As an illustration of the progressive nature of some palsies: (1) the right arm, left lower extremity, left arm, neck, right arm and right hand, were involved within two days. (2) Weakness of the lower extremities, paralysis of the left hand and paralysis of the right arm developed within six days, that is, from the fourth to the tenth day after inoculation. Deaths occurred on the ninth, eighth, fourteenth and sixteenth days, respectively, after inoculation.

The poliomyelitis virus produces in the brain of the monkey a nonpurulent inflammation. The virus prefers the gray matter, and the condition must be designated as a polioencephalitis. The inflammation involves both the mesodermal and the ectodermal tissues of the brain. The mesodermal response takes place largely in the perivascular sheaths of the vessels of the brain consisting of lymphocytes and polyblasts. The latter frequently migrate into the nervous tissue, where they produce so-called tissue nodes or penetrate the ectoderm diffusely. The

parenchyma of the brain and spinal cord sustains severe damage, being frequently digested by neuronophages.

For the classification of the polioencephalitis the pattern of the distribution of the inflammation in the central nervous system is deciding. The inflammation involves the spinal cord, medulla, brain stem and basal ganglions, as well as the motor region of the cortex. In some instances the entire parietotemporal region may be involved. The frontal and occipital regions usually escape.

The polioencephalitis shows the same histopathologic characteristics and pattern of distribution as human epidemic encephalitis, rabies, Borna's disease and American equine epidemic encephalitis.

INSENSIBLE LOSS OF BODY WEIGHT IN CHILDREN: OBSERVATIONS IN A CASE OF NEPHRITIS. DR. JOHN L. LAW, Ann Arbor, Mich.

Up to twenty years ago most of the observations on the insensible loss of body weight were made on adults. Since then considerable work has been done with infants and children. By the balance method it has been shown that, as in adults, the insensible loss is greater after food and exercise and less during sleep; it is moderately affected by the intake of fluids, but not by the average range of temperature or humidity or by clothes, if the clothes are not heavy enough to induce sweating. The insensible loss determined under basal conditions is thought to be dependable in predicting the metabolic rate of infants. It is probably applicable to other than basal conditions and to children as well as infants in the absence of visible perspiration. Levine has proposed normal basal standards of insensible loss for normal and dehydrated infants, referable to age, weight, height and surface area. In children both in normal health and with pathologic conditions the loss of heat through the evaporation of water is approximately 24 per cent of the total heat production, though minor variations have been found to occur in cases of eczema, diarrhea, marasmus, myxedema and other conditions. Most of the observations in children have been made under basal conditions in short periods. Newburgh has proposed a method of calculating the heat production in adults over long periods by determination of the daily insensible loss of water.

In this observation a diet closely approximating a maintenance diet was fed an 11 year old boy with subacute hemorrhagic nephritis who was free from symptoms. He was confined to bed under natural conditions. The room temperature was 70 F.; the humidity, 45 per cent, and there was no visible perspiration. The daily insensible loss of weight was determined and the insensible loss of water and heat production calculated from the metabolic mixture and from the diet.

For the seven day period the loss of heat by evaporation was 24.3 per cent, as calculated from the metabolic mixture, and 24.5 per cent, as calculated from the diet.

The method seems to offer a means of calculating the heat production accurately.
(The work was aided by a grant from the Mead Johnson Infant Research Fund.)

SEDIMENTATION RATE IN VARIOUS INFECTIOUS PROCESSES WITH SPECIAL REFERENCE TO METHOD EMPLOYED. DR. MARTIN BATTS, Ann Arbor, Mich.

That disease causes a variation in the suspension stability of the erythrocytes of the blood has been known since 1772, when Hewson demonstrated that the buffy coat or fibrin which appeared on the surface of the clotting blood shed by the phlebotomist was due simply to the rapid sinking of the erythrocytes before the blood had time to coagulate. But other factors besides disease can alter the sedimentation rate, and obviously the choice of the method of determination must depend on whether or not these factors have been ruled out. The method chosen in this study was that proposed by Plass and Rourke. The chief features of this method are that heparin is used to produce anticoagulation; results are expressed in millimeters per minute of most rapid settling, and correction is made for the varying percentage by volume of red cells in different bloods. The normal sedimentation rate varies from 0.08 to 0.35 mm. per minute.

Pregnancy is the only physiologic state that causes an elevation of the sedimentation rate. Pathologic causes of rapid sedimentation can be grouped under infection, malignancy, intoxication and trauma. Infection includes: (1) chronic infections, such as tuberculosis and syphilis; (2) acute infections, such as the exanthems, pneumonia and septicemia, and (3) suppurative processes, such as abscesses, empyema and pelvic inflammatory disease. All proved malignant processes were found to cause rapid sedimentation. Intoxication includes such conditions as anesthesia and heavy metal poisoning. Trauma as the cause of rapid sedimentation includes all processes in which there is destruction of tissue with absorption of necrotic or traumatized tissue. Conditions which were found to have no influence on the sedimentation rate are functional disturbances, uncomplicated metabolic diseases, simple catarrhal inflammations, chronic ulcerations of small extent, nonmalignant growths and focal infections which produce no constitutional disturbance. In general, uncomplicated allergic conditions cause slowing of the sedimentation rate.

The sedimentation rate is of definite value in diagnosis, treatment and prognosis. In diagnosis it is of use in determining the presence of organic disease, be it infection, a malignant process, intoxication or trauma; in aiding in the differentiation between organic and functional diseases, and in the differentiation between malignant and nonmalignant conditions. In prognosis repeated determinations indicate the degree of activity of disease processes. In treatment the efficacy of conservative treatment, such as rest in bed, for tuberculosis or fever; of therapy for pelvic inflammatory disease, or of surgical treatment, such as excision of malignant growths, with return to a normal rate after complete removal, and of roentgen therapy, with slowing of the rate in favorable cases and either no effect or acceleration in unfavorable cases, can be determined. The sedimentation rate is of only questionable value in the determination of the optimum time for operation, of a hemorrhagic diathesis in jaundice or of a thrombogenic predisposition in patients in whom pulmonary embolism develops.

Certain facts must be considered in evaluating the sedimentation rate: It does not determine the diagnosis of specific disease; it is elevated in pregnancy after the third month, and it reveals the presence of more types of pathologic processes than infection. A normal rate does not preclude the presence of disease, but it shows that disease, if present, is causing little, if any, constitutional disturbance.

ORGAN SPECIFICITY OF HUMAN TISSUE IN RELATION TO PROTEINURIA AS DETERMINED BY THE PRECIPITIN TEST. DR. D. MURRAY COWIE, Ann Arbor, Mich., and M. CATHERINE MAGEE, Ann Arbor, Mich.

We produced in rabbits antiserums to human kidney, liver, spleen and blood serum for the purpose of studying the question of organ tissue specificity in relation to proteinuria. It is believed by some that one can determine by means of the precipitin test whether protein in urine is coming from the kidney, the circulating blood or some other source, particularly the liver. Zinsser antedated the clinician when he remarked: "We have seen . . . how clinically slight the changes in a protein may be which can alter materially its antigenic nature, and it is a logical deduction that different organs of the same animal might contain antigenic constituents qualitatively different from the general serum protein."

Our human material was obtained at autopsies performed a few hours after death, the bodies having been kept in refrigeration during this time. Normal tissue, as well as tissue from patients with chronic nephritis, was selected. The antigens were prepared by precipitation of the carefully washed and ground tissue with ammonium sulphate and dialyzed against water to remove all free ammonia.

These observations were carried on with the hope of confirming those of Andrews and Thomas and those of Thomas, Schlegel and Andrews, who by venoclysis in dogs, using a hypertonic solution, so damaged the liver and kidney that albuminuria resulted. By means of the precipitin method they were able to demonstrate that the protein in the urine came from the damaged organs, for

example the liver. However, they did not report any observations to prove that their liver antiserum reacted only with liver antigen. From their observations they concluded that albuminuria in clinical nephritis may arise from a disorder of various organs of the body, and that the organ which causes it may be identified by the precipitin test. In the cases of artificial uremia which they produced "more than 100 samples of urine passed in the early states . . . were thus shown to contain no blood protein. . . . A protein foreign to the blood is excreted and . . . after a short time the renal epithelium is rendered permeable to normal proteins."

Our observations, which were extensive, showed that the antiserums produced by human serum and the kidney, liver and spleen are not specific. That is, kidney antiserum reacts equally well with liver and spleen antiserum, and vice versa. (The antigens and antiserums react well for as long as two months after preparation.) Diluted human serum reacts in exactly the same way when titrated against undiluted antigen, as do antiserums prepared from the liver, kidney and spleen; that is, the precipitin reaction is of equal strength. However, human serum titrated against human antiserum gives a stronger precipitin reaction than do the other tissue antigens.

We were successful in demonstrating two distinct proteins in our tissue antigens. Kidney and liver tissue antiserums treated with human serum antigen to the point where the supernatant fluid after centrifugation no longer gave a precipitin reaction showed a distinct precipitate when treated with kidney and liver antigen. We have further shown that all organ tissue antigens react alike; that is, the same amount of precipitate occurs with antigens prepared from the kidney, liver and spleen. There is no specificity. We have designated this substance as organ tissue protein.

To follow this a bit further, we carried out carefully, for our own satisfaction, efforts to produce homologous antiserums in rabbits by giving them injections of homologous serum, prepared from the liver, kidney and spleen. That is, normal rabbit antigens were injected into normal rabbits. The organs were removed immediately at death (caused by a blow) and preserved in dry ice to prevent any change in the tissue, such as might result from autolysis. (In all our work the strictest aseptic technic was used to prevent bacterial contamination of the antigens.) As we expected and as had been long ago determined, no specifically reacting antiserums developed. Nor were we able to demonstrate antiserums in rabbits given injections of homologous antigens prepared from rabbits dying of etherization, the idea being to denaturize the tissue protein.

From our work it seems evident that cross-precipitation reactions must be eliminated before the precipitin test can be used to identify specific tissue proteins. It also seems evident that the condition in the patient with nephritis is not comparable with that induced in dogs by venoclysis in which a hypertonic solution of sodium chloride is used. The usual disease causing proteinuria does not produce analogous destruction of tissue. It is, however, conceivable that any foreign protein escaping with the urine may be detected by means of the precipitin test.

PRELIMINARY REPORT ON PULMONARY TUBERCULOSIS AMONG BOYS AND GIRLS OF HIGH SCHOOL AGE IN THE CITY OF PHILADELPHIA. DR. PAUL B. KREITZ, Philadelphia.

This study, which was sponsored by the Henry Phipps Institute and the Philadelphia Health Society and Tuberculosis Committee, was undertaken to determine the extent and degree of tuberculosis in the adolescents of Philadelphia. Studies were limited to persons of this age group because of the greater incidence of tuberculosis in adolescence. The survey covered a period of three years (from 1931 to 1934).

There were 8,019 boys and girls ranging in age from 12 to 25 years. The majority were between 15 and 18 years of age. Tuberculin tests were not done, since we believed that their value was limited in older children. Roentgenograms of the chest were taken for all the subjects, and when active pulmonary lesions

were found follow-up serial roentgen studies were made. In interpreting the films we regarded pulmonary nodules, tracheobronchial calcification and strandlike nonapical lesions as evidence of latent and inactive infection. The soft flocculent and confluent patchy lesions in the apexes or parenchyma we considered as evidence of activity. Approximately 1 of every 6 or 16.7 per cent of the entire group, showed roentgenologic evidence of pulmonary tuberculosis. The process was inactive in 13.07 per cent of these and active in 298, or 3.72 per cent. Thus, 1 of every 27 of an unselected group of adolescent boys and girls had roentgen evidence of active pulmonary tuberculosis, though in most cases no clinical evidence of this disease was revealed either by the history or by physical examination.

In the group of those with active pulmonary tuberculosis 25 had grave, minimal or advanced lesions, and 5 of these died within the period of the survey. Eighty-six with active cases could not be followed. It was possible to carry out serial roentgen studies on 187 of the group of those with active cases. In 104, or 34.9 per cent, no change was noted. Fifty-five, or 18.5 per cent, showed improvement, and 28, or 9.4 per cent, showed progression. All were under medical supervision and care throughout the period of investigation.

I wish to stress the importance and necessity of detecting tuberculosis in its latent stage if proper supervision and control of the disease are to be hoped for. For this purpose accurate roentgenograms are indispensable. Physical examination at best is unreliable.

DEVELOPMENT OF HIGH TITERS OF RESISTANCE TO POLLEN ANTIGENS MAINTAINED OVER LONG PERIODS; ITS EFFECT IN THE TREATMENT OF HAY FEVER. DR. D. MURRAY COWIE, Ann Arbor, Mich., and DR. B. JIMENEZ, Ann Arbor, Mich.

Many examples are recorded, in our series of children and adults, of the taking of 0.5 cc. of pollen extracts in concentrations as high as 0.35 mg. per hundred cubic centimeters of solution (the so-called 1/33 extract). Such extracts result from dissolving 1 Gm. of dry pollen in 33 cc. of extracting solution. Children usually advance in resistance as rapidly as adults. Many maintain this high dosage at three and four weekly intervals for more than a year without showing any untoward symptoms. While the injection of such strong concentrations is not necessary, it is shown that patients tolerate them well, and frequently preseasonal doses do not have to be increased. Many patients go through the season satisfactorily without being obliged to resort to larger doses during the preseasonal short intervals. Perhaps a better plan is to maintain a dosage of 0.1 cc. of this concentration throughout the year and gradually increase it preseasonally by giving weekly doses.

MARKED GENERAL REACTION FOLLOWING INTRADERMAL TESTING: REPORT OF CASES. DR. D. MURRAY COWIE, Ann Arbor, Mich., and DR. B. JIMENEZ, Ann Arbor, Mich.

We selected 60 cases from our files. In 26, reactions could be accredited to a single allergen. In 34, reactions could be accredited to one or more allergens. The allergens causing the general reaction were, in order of their frequency: whole wheat, in 17 cases; coffee, in 9; silk, in 6; tea, in 5; pollens, in 3; yeast, in 3; kapok, in 3; pears, in 2; asparagus, in 2; cocoa, in 2; beets, in 2, and the following in 1—ginger, kidney beans, raspberries, apples, crabs, eggs, orris root, peas, almonds, bananas, tomatoes, sweet potatoes, rye, pumpkins, spinach, cat hair, black pepper, dog hair and red fox hair.

The clinical manifestations induced were: rhinitis, in 18 cases; asthma, in 15; headache, in 14; gastro-intestinal upsets (including vomiting and diarrhea), in 13; hives, in 12; cough, in 7; angioneurotic edema, in 6; migraine, in 4; pruritus, in 5; arthritis, in 3; epileptic attack, in 2; chills and aching, in 1; rash, in 1; backache, in 1, and pains in the joints, in 1. The administration of epinephrine hydrochloride was frequently necessary, as many of the reactions were severe.

Book Reviews

Periodic Fertility and Sterility in Woman: A Natural Method of Birth Control. By Prof. Dr. Herman Knaus, the German University of Prague. English translation by D. H. Kitchin and Kathleen Kitchin. Cloth. Price, $6 (15 marks); post-free, $6.50 (16.50 marks). Pp. 160, with 64 illustrations and 12 tables. Vienna: Wilhelm Maudrich, 1934.

The great present interest of the public and of at least a part of the medical profession in the subject of birth control has caused recent publications in the popular and medical press concerning the rhythmic or "natural" method of contraception to attract considerable attention.

This little monograph sets forth the hypothesis on which the author bases his technic for contraception and his method of indicating that period of the menstrual cycle during which conception can occur, and, conversely, that portion of the cycle during which impregnation may confidently be expected not to occur.

It has gradually come to be accepted that the life period and certainly the duration of the fertility of both the ovum and the sperm are less than was formerly supposed to be the case. Knaus discusses at some length the factors which govern the length of life of human sperms and concludes, on apparently sufficient grounds, that their viability cannot exceed forty-eight hours.

The processes concerned in ovulation are discussed, and the conclusion is reached and definitely set forth that the ovum is capable of fertilization for only a few hours after its escape from the follicle. This assertion is well buttressed by facts drawn from observations made on lower animals, as well as from the work of other investigators. If these hypotheses are accepted, and they are in accordance with accepted facts today, it remains only to determine the exact time of ovulation to solve rather completely the problem of contraception.

The difficulty in the application of the method to a large number of persons lies in the fact that it cannot be adopted offhand on a casual estimate of the menstrual cycle. Ovulation occurs regularly, according to Knaus, fifteen days before the onset of menstruation. This conclusion was arrived at by determining experimentally the time in the menstrual cycle at which the uterine muscle becomes insensitive to the action of pituitary because of the influence of the hormone of the corpus luteum.

Assuming the correctness of the author's idea of an exact relationship between the day of ovulation and the beginning of the succeeding menstruation, in order that the exact date of ovulation in an individual woman may be ascertained with a sufficient degree of accuracy for contraception to be based on it prolonged observation is necessary, the mere opinion of the woman not being sufficiently specific. In the author's words, "If we desire authentic information on the length and regularity of the menstrual cycle in one particular woman, we must no longer be content with her own recollection of the rhythm of her periods, but must insist on her noting the exact dates of menstruation for at least a year. That is the minimum information on which a trustworthy account can be given of the peculiarities of the menstrual cycle in a given individual."

A number of cases are cited, some of persons in the families of gynecologists who are friends of the author, in which failure to acquire thoroughly the requisite information led to failure.

Knaus holds that the rule that ovulation precedes menstruation by fifteen days is true in all types of menstrual cycles. Thus, in a twenty-eight day cycle ovulation occurs on the fourteenth day, in a twenty-six day cycle on the twelfth day and in a thirty day cycle on the sixteenth day. "In irregular cycles the ovulation date is that period of time which falls between the ovulation days of the shortest and longest cycle respectively, the cycles being recorded for at least 12 months."

If the day of ovulation is known, the time during which conception is possible, according to the author's rule, is the day of ovulation, three days before it and one day after it, or five days in all. In women whose cycle varies the entire possible period of ovulation must be included, plus three days before it and one day after it.

In regard to the author's opinion as to the shortness of the life of the sperm and ovum probably no controversy will arise today among qualified authorities. Hartman and Patten are also of the opinion that the sperm probably loses its fertilizing power before the end of its short life. These authors stated that controlled experimental evidence points to the fact that the ovum, once extruded from the ovary, is extremely short-lived. Other workers have agreed that ovulation occurs about midway in the menstrual cycle and that in a small number of women a cramping pain, *Mittelschmerz,* indicates the time. Whether the mathematically accurate fixation of the date will be generally accepted must await further work by other investigators. Ogino believes that the period of frequent conception is from the sixteenth to the twelfth day preceding the expected period.

Knaus provides a convenient menstrual calendar in booklet form which women who are interested may use for the assembling of necessary dates.

The monograph is an interesting account of work earnestly done, and the facts adduced must, on the whole, be credited. If the text assumes here and there a little of the polemic, this may be excused on the ground of the author's enthusiasm. The same may be said of the rather frequent use of the first personal pronoun. Even though the author's theory of an exact date of ovulation be accepted, one may wonder how practicable a method of contraception this may be.

The difficulty with which women in the outpatient department of the reviewer's service, in economic straits and with rapidly increasing families, are induced to make one visit to a birth control clinic causes him to wonder whether the necessity for prolonged and careful compilation of dates will not militate against the efficient use by a large number of women of the facts presented.

The book and menstrual calendars are obtainable from the Concip Company, Hobart, Indiana.

The British Pharmaceutical Codex, 1934. Fourth edition. Published by direction of the Council of the Pharmaceutical Society of Great Britain. Price, 35 shillings. Pp. 1667. London: The Pharmaceutical Press, 1934.

The object of the book is to provide formulas and descriptions of drugs and medicines not officially recognized in the British Empire, also of medicinal articles not in general use and not recognized by the British Pharmacopeia but still somewhat in demand, and of new articles which have not yet been recognized but are being used.

The book is published as a reliable reference work for the use of medical practitioners and pharmacists. It is a composite of the Dispensatory of the United States of America, the National Formulary and New and Nonofficial Remedies; it is a recipe book, which contains accurate information for prescribers and dispensers, especially those practicing in the British Empire.

It also includes the names of the principal substances and preparations which are official in the pharmacopeias of the United States, France and Germany, as well as of Great Britain.

The book is arranged in four parts, as follows: (1) monographs on chemical substances or drugs of vegetable and animal origin, (2) monographs on surgical dressings and the basic animal and vegetable fibers used in their manufacture, (3) galenical and other preparations of the Codex and (4) appendixes including tables, a list of general tests, reagents and methods of sterilization, a pharmacologic index, and a list of trade names and proprietary substances.

Mothers' Guide When Sickness Comes. By Roger H. Dennett and Edward T. Wilkes. Price, $2.50. Pp. 367. Garden City, N. Y.: Doubleday, Doran & Company, Inc., 1934.

Dennett and Wilkes have written a worthwhile book which should be of particular value to anxious mothers in communities with limited pediatric facilities.

There are general instructions about the care of well and sick children, a description of preventive measures, a list of poisons and antidotes and a list of special diets and recipes. There are instructions on the technic of isolation and special procedures, such as irrigation of the eyes, enemas and the inhalation of steam, which should help mothers carry out the physician's orders properly. The common ailments and the contagious diseases are considered, and emergencies, such as fractures, convulsions, fainting and injuries to the head, are discussed in a manner which ought to enable a parent to act properly and better evaluate the need for the physician's assistance.

The arguments against such a book are that many mothers are tempted to carry out medical treatment when thus aided, in spite of the authors' warning to the contrary, and that the ideas and instructions of many pediatricians may differ from some of the dogmatic statements contained in the book, which fact may or may not be confusing to the mother.

When used as a supplement to the physician's instructions, the book should prove valuable for reading in the home.

Konstitution und Tuberculose im Kindesalter. By Dr. Kurt Klare. Price, 4. marks. Pp. 42, with 32 illustrations. Leipzig: Georg Thieme, 1935.

Klare is thoroughly persuaded of (1) the existence of easily recognizable constitutional types and (2) the significance of such types in the prognosis of tuberculous infection. He believes that whereas bacteriologic and roentgenologic study of the disease have been of vital importance in the evolution of present knowledge concerning it, one should revert to a more careful clinical examination of the patient. Combining the concepts of the new era with those of the prebacteriologic days, one will better be able to search for the explanation of the contradictory facts that whereas 90 per cent or more of all persons become infected with tuberculosis, only a small percentage become clinically ill and comparatively few (one in one thousand per annum) die of this disease. Whereas Klare's thesis is of some significance, the practical difficulty of defining a clearcut physical status and of reconciling the numerous exceptions to any given rule will always confront one.

Klimatische Kuren im Kindesalter. By Prof. Dr. Rudolf Degkwitz. Price, 1.20 marks. Pp. 32. Leipzig: Georg Thieme, 1934.

In this treatise climatic cures for children are discussed from a rational and intelligent point of view. Degkwitz emphasizes the fact that in most children it is the altered routine and the change in climate that produce beneficial effects, rather than the specific properties of the climate alone. However, there are certain climatic factors, such as the amount of sunshine, the humidity, the altitude, the temperature and the wind, which should be taken into consideration in choosing the climate most favorable for certain illnesses. In some instances the degree of severity of the illness may be the deciding factor in the choice of climate. The basic principles involved in determining the proper climate for an individual child are thoroughly analyzed. The illnesses chiefly considered by the author are nervous disorders, allergic diseases, cardiac diseases, respiratory infections and tuberculosis. This monograph offers a great deal of practical value to the physician who is called on to advise patients concerning climatic cures.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Professor G. Scheltema, 6a Heereplein, Groningen, The Netherlands.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.
Place: Bâle, Switzerland: Time: September 1935.

FOREIGN

British Paediatric Association

President: Dr. Hugh Thursfield, 84, Wimpole St., London, W. 1.
Secretary: Dr. Arthur G. Maitland Jones, 31 A, Weymouth St., London, W. 1.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. R. C. Jewesbury, 5, Wimpole St., London, W. 1.
Secretary: Dr. Helen Mackay, 28, John St., London, W. C. 1.
Place: 1, Wimpole St., London. Time: Fourth Friday of each month, 4: 30 p. m.

Paediatrický Spolok na Slovensku

President: Dr. A. J. Chura, Lazaretská 6, Bratislava, Czechoslovakia.
Secretary: Dr. S. Limbacher, Dlhá 2, Bratislava, Czechoslovakia.
Place: Pediatric Clinic, University, Bratislava. Time: Six times a year.

NATIONAL

American Medical Association, Scientific Assembly, Section on Diseases of Children

Chairman: Dr. A. Graeme Mitchell, Children's Hospital, Cincinnati.
Secretary: Dr. Ralph M. Tyson, 334 S. 21st St., Philadelphia.
Place: Atlantic City, N. J. Time: June 10-14, 1935.

American Academy of Pediatrics

President: Dr. Thomas B. Cooley, 1728 Seminole Ave., Detroit.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.
Place: New York. Time: June 7-8, 1935.
Region I. Place: Philadelphia. Time: Oct. 11-12, 1935.
Regions II and III. Place: St. Louis. Time: Fall, 1935.
Region IV. Place: Seattle, with North Pacific Pediatric Society. Time: Aug. 9-10, 1935.

American Child Health Association

President: Dr. Samuel McC. Hamill, 1822 Spruce St., Philadelphia.
Secretary: Dr. Philip Van Ingen, 125 E. 71st St., New York.

American Hospital Association, Children's Hospital Section

President: Mr. Robert Witham, Children's Hospital, Denver.
Secretary: Miss Agnes O'Roke, Kosair Crippled Children's Hospital, Louisville, Ky.

American Pediatric Society

President: Dr. Borden S. Veeder, 3720 Washington Ave., St. Louis.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.

Canadian Society for the Study of Diseases of Children

President: Dr. D. P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary-Treasurer: Dr. R. R. Struthers, 1414 Drummond St., Montreal.
Place: Buffalo, N. Y. Time: June 1935.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Joseph Stokes Jr., Children's Hospital, Philadelphia.
Secretary: Dr. A. A. Weech, Babies Hospital, New York.

SECTIONAL

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Armin Rembe, Stimson Bldg., Seattle.
Secretary: Dr. Frank H. Douglass, 1227 Medical and Dental Bldg., Seattle.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON PEDIATRICS

Chairman: Dr. Oliver W. Hill, 301 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. Madison Hines Roberts, 104 Ponce de Leon Ave., N. E., Atlanta, Ga.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. Charles Abbott, 1817 Broad St., Tuscaloosa.
Secretary-Treasurer: Dr. Wallace Clyde, Employees' Hospital, Fairfield.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Cairman: Dr. Morgan Smith, 625 Beech St., Little Rock.
Secretary: Dr. Madeline A. M. Melson, 2111 N. Spruce St., Little Rock.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Benjamin Bashinski, 700 Spring St., Macon.
Secretary-Treasurer: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. Lonis H. Segar, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Matthew Winters, 23 E. Ohio St., Indianapolis.
Time: Two meetings a year.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. Charles James Bloom, 3439 Prytania St., New Orleans.
Secretary-Treasurer: Dr. J. A. Crawford, 834 Ryan St., Lake Charles.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. George Sincerbeaux, 6 William St., Auburn.
Secretary: Dr. John D. Craig, 12 E. 11th St., New York.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Edgar E. Martmer, 749 David Whitney Bldg., Detroit.
Secretary: Dr. C. R. Dengler, 131 W. Michigan Ave., Jackson.
Place: Flint. Time: September 1935.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. N. C. Womack, Jackson Infirmary, Jackson.
Secretary-Treasurer: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Place: To be designated by Society. Time: Yearly.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. J. A. Henske, 1614 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. J. H. Murphy, 915 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. J. Buren Sidbury, 15 N. Fifth St., Wilmington.
Secretary: Dr. E. K. McLean, 121 W. Seventh St., Charlotte.
Place: Various children's hospitals. Time: Twice a year.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. C. V. Rice, 222 Wall St., Muskogee.
Secretary: Dr. B. H. Nicholson, 301 N. W. Twelfth St., Oklahoma City.

PENNSYLVANIA MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Francis T. O'Donnell, 345 North Main St., Wilkes-Barre.
Secretary: Dr. Theodore O. Elterich, 119 S. Highland Ave., Pittsburgh.
Place: Harrisburg. Time: Sept. 30-Oct. 3, 1935.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. William Weston Jr., 1428 Lady St., Columbia.
Secretary-Treasurer: Dr. Leland B. Salters, 317 S. Warley Ave., Florence.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Joe T. Smith, 702 Medical Arts Bldg., Knoxville.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Place: Memphis. Time: April 1936.

TEXAS PEDIATRIC SOCIETY

President: Dr. Ramsay H. Moore, 3600 Fairmount St., Dallas.
Secretary-Treasurer: Dr. F. H. Lancaster, Medical Arts Bldg., Houston.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. W. P. McDowell, 142 W. York St., Norfolk.
Secretary: Dr. W. A. McGee, 616 W. Grace St., Richmond.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. R. C. Hood, 428 W. Pike St., Clarksburg.
Secretary: Dr. Russell C. Bond, 1325 Chapline St., Wheeling.

LOCAL

ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harry M. Greenwald, 499 Ocean Ave., Brooklyn.
Secretary: Dr. Sylvan D. Lazarus, 847 Lincoln Place, Brooklyn.
Place: Medical Society of County of Kings Bldg., 1313 Bedford Ave., Brooklyn.
Time: Third Wednesday of each month from October to May, 8:30 p. m.

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. A. Garvin, Carnegie Medical Bldg., Cleveland.
Secretary: Dr. William M. Champion, 2323 Prospect Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. C. V. Mulligan, 17 Walmer Rd., N., Toronto.
Secretary: Dr. T. B. Verner, 170 St. George St., Toronto.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry M. Shapiro, 1882 Grand Concourse, New York.
Secretary: Dr. Daniel J. Dolan, 420 E. 159th St., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. W. F. Watton, 240 Berkeley Pl., Brooklyn.
Secretary: John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Stanley Gibson, 9503 Prospect Ave., Chicago.
Secretary: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Place: John B. Murphy Memorial Bldg. Time: Third Tuesday of each month

DALLAS COUNTY PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas, Texas.
Secretary: Dr. R. S. Usry, 1835 Garrett Ave., Dallas, Texas.
Place: Bradford Memorial Hospital. Time: 1 p. m., first and third Saturdays of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Earl W. May, 1551 Woodward Ave., Detroit.
Secretary: Dr. E. A. Wishropp, 10 Peterboro Ave., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month.

FULTON COUNTY MEDICAL SOCIETY, PEDIATRIC SECTION (ATLANTA, GA.)

Chairman: Dr. Joseph Yampolsky, 478 Peachtree St., Atlanta.
Secretary: Dr. T. I. Willingham, 384 Peachtree St., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Frank Lancaster, Medical Arts Bldg., Houston, Texas.
Secretary-Treasurer: Dr. A. A. Little Jr., 817 Holman Ave., Houston, Texas.
Place: Houston Club: Time: Third Monday of each month.

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Helmina Jeidell, 11 Exchange Pl., Salt Lake City, Utah.
Secretary-Treasurer: Dr. Edwin R. Murphy, 9 Exchange Pl., Salt Lake City, Utah.
Place: Salt Lake City, General Hospital. Time: First Thursday of each month, 8 p. m.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1103 Grand Ave., Kansas City.
Secretary: Dr. S. A. Stadler, 6133 Brookside Blvd., Kansas City.
Place: Kansas City General Hospital. Time: On call.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. Henry A. Reisman, 148, 88th Ave., Jamaica, L. I.
Secretary-Treasurer: Dr. Edith A. Mittell, 112 Queens Blvd., Forest Hills, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y.: Time: Third Monday of October, January, March and May.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. Harry J. Jacobson, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Clyde V. Croswell, 1052 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month, except June, July and August, 8 p. m.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. J. Gurney Taylor, 324 E. Wisconsin St., Milwuakee.
Secretary: Dr. H. B. Miner, 425 E. Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Paul Emerson, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Henry E. Gallup, 66 Commonwealth Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Harry Bakwin, 132 E. 71st St., New York.
Secretary: Dr. Alexander T. Martin, 107 E. 85th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. O. W. Rowe, 205 W. 2nd St., Duluth, Minn.
Secretary: Dr. E. F. Robb, 1801 Lyndale Ave., S., Minneapolis.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. John D. Donnelly, 115 Bryn Mawr Ave., Bala, Pa.
Secretary: Dr. James E. Bowman, 4091 Comly St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to June, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. Carl K. Wagener, Jenkins Arcade, Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200 Fifth Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Tuesday, alternate months from October to April, inclusive.

RICHMOND PEDIATRIC SOCIETY

President: Dr. W. A. McGee, 616 W. Grace St., Richmond, Va.
Secretary-Treasurer: Dr. Emily Gardner, 1100 W. Franklln St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: First Thursday of each month (except July, August and September).

ROCHESTER PEDIATRIC SOCIETY

President: Dr. H. F. Rowley, 176 S. Goodman St., Rochester, N. Y.
Secretary: Dr. J. M. Parker, 26 S. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Ralph Verploeg, 1850 Gilpin St., Denver.
Secretary: Dr. Max M. Ginsburg, Metropolitan Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 2:30 p. m.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. J. V. Cooke, St. Louis Children's Hospital, St. Louis.
Secretary-Treasurer: Dr. Katherine Bain, Beaumont Bldg., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Arthur E. Wade, 1215, 4th Ave., Seattle.
Secretary: Dr. Walter B. Seelye, Cobb Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Victor E. Stork, 1136 W. Sixth St., Los Angeles.
Secretary: Dr. Howard R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Daniel Budson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Place: Ann Arbor, Mich. Time: Nov. 22-23, 1935.

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